BMJ Open

Pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048478
Article Type:	Original research
Date Submitted by the Author:	28-Dec-2020
Complete List of Authors:	O Murchu, Eamon; Health Information and Quality Authority; Trinity College Marshall, Liam; Health Information and Quality Authority Teljeur, Conor; Health Information and Quality Authority Harrington, Patricia; Health Information and Quality Authority Hayes, Catherine; University of Dublin Trinity College, Public Health and Primary Care Moran, Patrick; Health Information and Quality Authority; Trinity College Ryan, Mairin; Health Information and Quality Authority; Trinity College, Department of Pharmacology & Therapeutics
Keywords:	Epidemiology < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations

Authors: Eamon O Murchu, MD, MPH;[a, b] Liam Marshall, MSc; [a] Catherine Hayes, MD, MPH, MB;[b] Patricia Harrington, PhD;[a] Patrick Moran, PhD;[a, b] Conor Teljeur, PhD;[a] Máirín Ryan, PhD.[a, c]

[a]Health Information and Quality Authority, George's Court, George's Lane, Dublin 7, Ireland

[b]Trinity College Dublin, Institute of Population Health, Tallaght, Dublin 24, Ireland

[c]Trinity College Dublin, Department of Pharmacology & Therapeutics, Trinity Health Sciences, Dublin 8, Ireland

Corresponding author: Eamon O Murchu. Health Information and Quality Authority, George's Court, George's Lane, Dublin 7, Ireland. eomurchu@hiqa.ie, Tel: +353838818554.

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None declared.

Data sharing: All data relevant to the study are included in the article or uploaded as supplementary information.

Keywords: PrEP; HIV; systematic review; sexually transmitted infections; sexual behaviour.

Word count: Abstract=296; Main text (excluding abstract, tables, figures, references): 3,906.

Figures=4; **Tables**=4; **Supplementary Material**=2 (S1. Protocol, S2. Additional results)

PRISMA Checklist=1

Abstract

Objective

To conduct a systematic review and meta-analysis of randomised controlled trials (RCTs) on the effectiveness and safety of Pre-Exposure Prophylaxis (PrEP) to prevent HIV.

Methods

Oral tenofovir-containing PrEP was compared with placebo, no treatment or alternative medication/dosing schedule. The primary outcome was HIV incidence and secondary outcomes were adherence, adverse events, 'risk compensation' (an increase in risky sexual behaviour) and incidence of other sexually transmitted infections (STIs).

Databases were searched up to 5 July 2020. Quality of individual studies was assessed using the Cochrane Risk of Bias tool and the certainty of evidence was assessed using GRADE. All analyses were stratified a priori by population: men who have sex with men (MSM), serodiscordant couples, heterosexuals and people who inject drugs (PWID). PROSPERO ID: CRD42017065937.

Results

Of 2,803 unique records, 15 RCTs met our inclusion criteria. Over 25,000 participants were included, encompassing 38,289 person-years of follow-up data. All individual studies were at low risk of bias.

PrEP was found to be effective in MSM (Relative Risk [RR] 0.25, 95% CI: 0.1-0.61, 5,103 person-years of data, high certainty evidence), serodiscordant couples (RR 0.25, 95% CI: 0.14-0.46, 5,237 person-years, high certainty evidence) and PWID (RR 0.51, 95% CI: 0.29-

0.92, 9,666 person-years, moderate certainty evidence), but not in heterosexuals (non-significant).

With high adherence (≥80%), RR in MSM was reduced to 0.14 (95% CI: 0.06 to 0.35). Efficacy was strongly associated with adherence (p<0.01). PrEP was found to be safe, however unrecognised acute HIV at enrolment increased the risk of viral drug mutations (RR 3.53, 95% CI: 1.18 to 10.56). Evidence for risk compensation or an increase in STIs was not found.

Conclusions

PrEP is safe and effective in MSM, serodiscordant couples and PWID. Additional research is needed prior to recommending PrEP in heterosexuals. Effectiveness is strongly associated with adherence.

Article Summary

Strengths and limitations of this study

- A systematic review and meta-analysis of RCTs was conducted in adherence with PRISMA guidelines
- The quality of evidence was assessed using the GRADE framework
- The study assisted the development of clinical practice guidelines on HIV prevention in Ireland and informed the decision of the Irish government to implement a national PrEP programme
- Going forward, the proposed PrEP programme must be accompanied by ongoing monitoring and surveillance to ensure the high efficacy reported in RCTs translates into real-world effectiveness.

Introduction

While the incidence of HIV has declined worldwide over the past decade, there were still 1.7 million new HIV infections in 2018,[1] highlighting the ongoing need for new and effective HIV prevention initiatives. Pre-exposure prophylaxis (PrEP) is a novel biomedical form of HIV prevention method, whereby oral anti-retrovirals (most commonly a combination of tenofovir and emtricitabine) are taken by individuals at high risk of HIV acquisition to prevent infection. PrEP aims to complement the existing arsenal of HIV prevention strategies, such as the promotion of safer sex practices, treatment-as-prevention and post-exposure prophylaxis after sexual exposure.

In 2014, the WHO recommended offering PrEP to men who have sex with men (MSM),[2] based a 2010 trial that demonstrated the effectiveness in this group.[3] Subsequently, in 2015, they broadened the recommendation to include anyone at substantial risk of HIV infection (defined as risk of 3 per 100 person-years in the absence of PrEP),[4] based on further evidence of the acceptability and effectiveness in other populations. While the success of early PrEP studies in MSM was replicated in the years that followed, uncertainty still exists in other key populations. Many initial studies that failed to demonstrate effectiveness were plagued by poor adherence, such as those that enrolled heterosexual women. Also, of major concern to public health officials and policy-makers is the potential occurrence of 'risk compensation' in PrEP users (an increase in unsafe sexual practices due to the knowledge that PrEP is protective against HIV), which may lead to an increase in STIs, exacerbating the secular trend of rising STI rates in many countries.

Since the most recent WHO recommendation, a number of new trials in diverse populations

have been conducted. We therefore conducted a systematic review and meta-analysis to retrieve the most up-to-date evidence on the effectiveness and safety of PrEP in all populations, with a particular emphasis on adherence and risk compensation. This review aimed to inform the decision of the Irish government to implement a PrEP programme and to assist in the development of national clinical practice guidelines on PrEP for HIV prevention.

Methods

A systematic review and meta-analysis was conducted, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5] The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[6] This framework is commonly used internationally to aid decisions by policy-makers, and ensured a systematic and transparent approach in the development of clinical practice recommendations. This study was registered with PROSPERO (ID: CRD42017065937) and followed a study protocol (Supplementary Material 1).

Search strategy and selection criteria

Electronic searches were conducted in Medline (PubMed), Embase, the Cochrane Register of Controlled Trials, CRD DARE Database, Morbidity and Mortality Weekly Report (CDC), and Eurosurveillance reports. Hand-searching of journals was also performed. Searches were conducted on 5 July 2020 (Supplementary Material 2). Only peer-reviewed studies with published full texts were included. No restrictions were placed based on location of the intervention or date of publication. No language restrictions were used; articles in languages other than English were translated where necessary. Table 1 outlines the inclusion criteria for study selection. Animal studies, studies that did not report primary outcome data (HIV incidence), and abstracts from conference proceedings were excluded.

It was decided a priori that all analyses would be stratified by population. The four populations were men who have sex with men (MSM), serodiscordant couples, heterosexuals and people who inject drugs (PWIDs).

Table 1. Inclusion criteria

Criteria for study selection	
Population	Anyone at elevated risk of HIV acquisition. Populations defined a priori: men who have sex with men, serodiscordant couples, heterosexual individuals, people who inject drugs
Intervention	Oral tenofovir-containing pre-exposure prophylaxis
Comparator	Placebo, no treatment or alternative oral PrEP medication/dosing schedule
Outcomes	Primary outcome: HIV incidence Secondary outcomes: 1. Adherence to PrEP 2. Adverse events 3. Incidence of other STIs and behaviour change associated with PrEP administration 4. Viral drug mutations among those who contract HIV
Studies	RCTs

Legend: PrEP – pre-exposure prophylaxis, RCT – randomised controlled trial, STI – sexually transmitted infection.

Data collection and analysis

Results of the database search was exported to Endnote X7. Full text articles were obtained for all citations identified as potentially eligible. Two reviewers (EOM and LM) independently screened these according to the pre-specified inclusion criteria. Supplementary Material 2 provides additional details on the data collection, management and analysis plan per the study protocol. Two reviewers (EOM and LM) independently performed data extraction and assessed the risk of bias according to the Cochrane Risk of Bias tool.[7] An overall assessment of the quality of the evidence was assessed using the GRADE approach that included an assessment of other biases, such as publication bias.[6]

Outcome measures for dichotomous data were calculated as risk ratios (RRs) with 95% confidence intervals (CIs). The risk of HIV infection represents the number of HIV infections that occurred per person-years of follow up data, and the RR represents the risk of HIV

infection in the PrEP group compared with control. A modified intention-to-treat approach was used in all analyses — the denominator in this case represents the total post-randomisation number less the number of participants found to be HIV positive at enrolment.

Clinical heterogeneity was assessed by the reviewers based on the description of the interventions and comparators in the RCTs. Statistical heterogeneity was examined using the I^2 statistic. If there was sufficient clinical homogeneity across studies, results were pooled using a random effects Mantel–Haenszel model. In analyses that included studies with no events in one or both arms, a sensitivity analysis was undertaken using a beta-normal Bayesian meta-analysis model.[8] All statistical analysis was performed in Review Manager 5.3 and R version 3.6.2.

In the estimation of PrEP effectiveness, subgroups of studies were defined by dosing schedule, comparator and adherence. Analyses were stratified by population and adherence. Plasma drug monitoring was favoured over self-report/pill count in the assessment of adherence (minimising recall bias); trials where ≥80% of participants adhered to the study medication were deemed 'high adherence' and <80% 'low adherence'. To investigate the relationship between efficacy and adherence, a meta-regression analysis was conducted in R version 3.6.2 (meta-regression was considered the appropriate model as it accounts for trial size in analyses). In the assessment of the safety of PrEP, the definitions for adverse events and serious adverse events followed the definitions used in the primary studies. In the assessment of behaviour change, the effect of PrEP on condom use, number of sexual partners, recreational drug use and the rate of new STI diagnoses (as a proxy for condomless sex) were assessed. In the assessment of PrEP-related drug mutations,

subgroups included patients with unrecognised acute HIV infection at the time of enrolment and patients who seroconverted during the course of the trial. Where there was a lack of data or agreed definitions for these outcomes, a narrative review was performed.

Results

A total of 2,803 unique records were retrieved, resulting in 73 studies for full text review (Figure 1 provides the PRISMA diagram of study selection and the list of excluded studies, along with reasons, is provided in Supplementary Material 3.1). Fifteen RCTs met our inclusion criteria and were included in the assessment of effectiveness and safety. Seven RCTs were placebo-controlled trials that evaluated daily oral PrEP.[3 9-14] Two studies randomised participants to receive either immediate or delayed PrEP.[15 16] Three placebo-controlled trials investigated non-daily PrEP, including intermittent and 'on-demand' (also known as event-based) PrEP.[17-19] Two RCTs did not contain a 'no PrEP' arm (placebo or no medication): one compared tenofovir with tenofovir/emtricitabine[20] and one compared three different PrEP dosing schedules.[21] One study contained three arms: PrEP, placebo and 'no pill'.[22] Four distinct patient populations were assessed. Six RCTs enrolled MSM,[3 15-18 22] five enrolled heterosexual participants,[10-12 14 21] three enrolled serodiscordant couples[13 19 20] and one enrolled PWIDs.[9]

Figure 1. PRISMA diagram of study selection

Figure 1 Legend: Diagram provides details on the selection process of studies for inclusion

Included studies involved 25,051 participants encompassing 38,289 person-years of follow-up data. Of the 15,062 participants that received active drug in the intervention arms of trials, 55% received combination tenofovir/emtricitabine and 45% received single agent tenofovir. Follow-up periods ranged from 17 weeks to 6.9 years. Four trials were conducted in high-income countries (USA, England, France and Canada), 10 in low- or middle-income countries (including nine trials in sub-Saharan Africa) and one was a multicenter trial

conducted across four continents. The main characteristics of included studies are provided in Table 2.

Table 2. Study characteristics

Study	Location	Population	Intervention	Comparison	Number of participants	Follow-up (person years)
MSM						
Hosek 2013 (Project PrEPare)[22]	United States	Young MSM. Median age: 19.97 years (range: 18–22)	Tenofovir/emtricitabine	Daily PrEP with placebo and 'no pill'	58	27
Grohskopf 2013 (CDC Safety Study)[15]	United States	MSM. Age range: 18–60 years	Tenofovir	Immediate/delayed PrEP with immediate/delayed placebo. 1:1:1:1 trial design: tenofovir, placebo, delayed tenofovir and delayed placebo groups	400	800
iPrEx (Grant 2010)[3]	Peru, Ecuador, South Africa, Brazil, Thailand, and United States	MSM and transgender women. Age range: 18–67 years. Sex: 100% male at birth; 1% female gender identity	Tenofovir/emtricitabine	Daily PrEP with placebo	2499	3324
McCormack 2015 (PROUD)[16]	England	MSM. Median age: 35 years Sex: 100% men	Tenofovir/emtricitabine	Immediate PrEP with delayed PrEP	545	504
Molina 2015 (IPERGAY)[17]	France and Canada	MSM. Median age 35 PrEP group, 34 placebo group; Sex: 100% men	Tenofovir/emtricitabine	Intermittent ('on demand') PrEP with placebo. Participants were instructed to take a loading dose of two pills of tenofovir-emtricitabine or placebo 2 to 24 hours before sex, followed by a third pill 24 hours after the first drug intake and a fourth pill 24 hours later*	400	431

Study	Location	Population	Intervention	Comparison	Number of participants	Follow-up (person years)
Mutua 2012 (IAVI Kenya Study)[18]	Kenya	Female sex workers and MSM. Mean age: 26 years (range: 18–49); Sex: 67 men; 5 women	Tenofovir/emtricitabine	Daily/intermittent PrEP to daily /intermittent placebo	72	24
Serodiscordant couples						
Kibengo 2013 (IAVI Uganda Study)[19]	Uganda	Serodiscordant couples. Mean age: 33 years (range: 20–48); Sex: 50% women; 50% men	Tenofovir/emtricitabine	Daily/intermittent PrEP with daily/intermittent placebo	72 couples	24
Baeten 2012 (Partners PrEP Study)[13]	Kenya and Uganda	Serodiscordant couples. Age range: 18–45 years; Sex: seronegative partner was male in 61–64% of couples (depending on group assignment)	Tenofovir/emtricitabine and tenofovir only (three arms: two active arms and one placebo arm)	Daily PrEP with placebo	4,747 couples	7,830
Baeten 2014 (Partners PrEP Study Continuation)[20]	Kenya and Uganda	Serodiscordant couples. Age range: 28–40 years; Sex: 62–64% men (depending on group assignment)	Tenofovir/emtricitabine and tenofovir (Two Active Arms)	Tenofovir/emtricitabine combination versus tenofovir	4,410 couples	8,791
Heterosexuals						
Bekker 2018 (ADAPT Cape Town)[21]	South Africa	Women and transgender males. Median age of women was 26 years (IQR 21–37; range 18–52)	Tenofovir/emtricitabine	Daily, time and event-driven PrEP≠	191	99

Study	Location	Population	Intervention	Comparison	Number of participants	Follow-up (person years)
Marrazzo 2015 (VOICE)[14]	South Africa, Uganda, and Zimbabwe	Women. Median age: 24 years (range: 18–40); Sex: 100% women	5 arms: tenofovir/emtricitabine, tenofovir only and 1% tenofovir vaginal gel (compared with placebo oral PrEP and placebo vaginal gel)	Daily PrEP with placebo	4,969	5,509
Peterson 2007 (West African Safety Study)	Nigeria, Cameroon, and Ghana	Women. Age range: 18–34 years; Sex: 100% women (mostly sex workers)	Tenofovir	Daily PrEP with placebo	936	428
Thigpen 2012 (TENOFOVIR2)[11]	Botswana	Heterosexual men and women. Age range: 18–39 years; Sex: 54.2% men; 45.8% women	Tenofovir/emtricitabine	Daily PrEP with placebo	1219	1,563
VanDamme 2012 (FEM-PrEP)[10]	Tanzania, South Africa, and Kenya	Women. Median age: 24.2 years (range: 18–35); Sex: 100% women	Tenofovir/emtricitabine	Daily PrEP with placebo	2,120	1407
PWIDs						
Choopanya 2013 (Bangkok Tenofovir Study)[9]	Thailand (Bangkok)	PWID. Median age: 31 years (range: 20–59) 80% male	Tenofovir	Daily PrEP with placebo	2,413	9,665

Table 1 Legend: MSM = men who have sex with men; PWID = people who inject drugs. Tenofovir = Tenofovir Disoproxil Fumarate. In all cases, tenofovir dose was 300mg and emtricitabine dose was 200mg. *In case of multiple consecutive episodes of sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse and then to take the two postexposure pills

Effectiveness

A meta-analysis of all trials that compared the effectiveness of PrEP to prevent HIV acquisition with control (placebo or no drug) is presented in Figure 2. A RR of 0.41 (95% CI: 0.26 to 0.67) was obtained, indicating a 59% reduction in the risk of HIV acquisition. This figure is subject to significant heterogeneity (I^2=79%).

Figure 2. Meta-analysis of all trials, PrEP versus placebo or no drug

Figure 2 Legend: Forest plot of the meta-analysis of HIV incidence in all trials, PrEP versus placebo or no drug

All included individual RCTs were judged to have a low risk of bias by the Cochrane Risk of Bias Tool (risk of bias graph and summary provided in Supplementary Material 3.2). Across studies, while publication bias may have been present in earlier, industry-funded studies (with fewer participants), this form of bias was considered less likely in the more recent, larger, publicly-funded studies.

Adherence by plasma drug detection varied greatly across studies, ranging from 25% to 88% (Supplementary Material 3.3).

The following sections present the effectiveness of PrEP to prevent HIV acquisition by study population and stratified by adherence, where appropriate. Tables 3 and 4 present the GRADE 'summary of findings' assessment of the effectiveness and safety of PrEP.

Table 3. GRADE summary of findings: PrEP effectiveness

Summary of findings table: Effectiveness of PrEP

Patient or population: HIV prevention in participants at substantial risk
Intervention: PrEP
Comparison: no PrEP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no PrEP	Risk with PrEP				
HIV infection: MSM (all clinical trials)	40 per 1,000	**10 per 1,000** (4 to 24)	**RR 0.25** (0.10 to 0.61)	5,103 (6 RCTs)	⨁⨁⨁⨁ HIGH [a, b]	PrEP is effective in preventing HIV acquisition in MSM with a risk reduction of 75%
HIV infection: MSM, trials with high (≥80%) adherence	66 per 1,000	**9 per 1,000** (4 to 23)	**RR 0.14** (0.06 to 0.35)	960 (3 RCTs)	⨁⨁⨁⨁ HIGH	PrEP is highly effective in preventing HIV acquisition in MSM in trials with high adherence (over 80%) with a risk reduction of 86%
HIV infection: Serodiscordant couples	20 per 1,000	**5 per 1,000** (3 to 9)	**RR 0.25** (0.14 to 0.46)	5,237 (2 RCTs)	⨁⨁⨁⨁ HIGH	PrEP is effective in preventing HIV acquisition in serodiscordant couples with a risk reduction of 75%
HIV infection: Heterosexual transmission	41 per 1,000	**32 per 1,000** (19 to 53)	**RR 0.77** (0.46 to 1.29)	6,821 (4 RCTs)	⨁⨁⨁◯ LOW[a, c]	PrEP is not effective in preventing heterosexual HIV transmission (all trials)
HIV infection: People who inject drugs	7 per 1,000	**3 per 1,000** (2 to 6)	**RR 0.51** (0.29 to 0.92)	9,666 (1 RCT)	⨁⨁⨁◯ MODERATE[d]	PrEP is effective in preventing HIV transmission in people who inject drugs with a risk reduction of 49%

Table 3 Legend:
Explanations
a. Downgraded one level for heterogeneity b. Upgraded one level for large effect (RR<0.5) c. Downgraded one level for imprecision d. Downgraded one level for indirectness
***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 4. GRADE summary of findings: Safety of PrEP

Summary of findings table: Safety of PrEP

Patient or population: HIV prevention in participants at substantial risk. **Intervention**: PrEP. **Comparison**: no PrEP.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no PrEP	Risk with PrEP				
Safety outcome: Any adverse event	776 per 1,000	**784 per 1,000** (768 to 799)	**RR 1.01** (0.99 to 1.03)	17,358 (10 RCTs)	⊕⊕⊕⊕ HIGH	Adverse events do not occur more commonly in patients taking PrEP compared with placebo. Adverse events were common in trials (78% of patients reporting 'any' event).
Safety outcome: Serious adverse events	81 per 1,000	**73 per 1,000** (60 to 91)	**RR 0.91** (0.74 to 1.13)	17,778 (12 RCTs)	⊕⊕⊕⊕ HIGH	Serious adverse events do not occur more commonly in patients taking PrEP compared with placebo. Serious adverse events occurred in 7% of patients in trials but most were not drug related.
Safety outcome: Deaths	13 per 1,000	**10 per 1,000** (8 to 15)	**RR 0.83** (0.60 to 1.15)	12,720 (11 RCTs)	⊕⊕⊕◯ MODERATE[a]	Deaths did not occur more commonly in people taking PrEP compared with placebo in trials. No deaths were related to PrEP.
Safety outcome: Drug resistance mutations in patients with acute HIV at enrolment	53 per 1,000	**174 per 1,000** (62 to 435)	**RR 3.30** (1.17 to 8.27)	44 (5 RCTs)	⊕⊕⊕◯ MODERATE[a]	Patients randomised to receive PrEP who had acute HIV at enrolment were at increased risk of developing resistance mutations to the study drug. Most conferred resistance to emtricitabine.

Table 4 Legend:
Explanations
a. Imprecision was detected due to few observations.
Note that only a minority of studies tested for viral drug resistance mutations
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Effectiveness in MSM

Six studies enrolled MSM. A meta-analysis of all studies resulted in a RR of 0.25 (95% CI: 0.1 to 0.61), indicating a 75% reduction in the risk of HIV acquisition (Figure 3). PrEP was most effective in studies with high adherence, as expected, where risk of HIV acquisition was reduced by 86%. When adherence was under 80%, risk of acquisition was reduced by 45%. Under alternative models, such as a beta-binomial and beta-normal (to account for trials with no events in either arms), the confidence bounds for the RR include the line of no effect in the poor adherence group.

Figure 3. Meta-analysis: HIV acquisition in MSM, all studies

Figure 3 Legend: Forest plot of the meta-analysis of HIV incidence in all MSM trials, PrEP versus placebo or no drug. Subgroups include high (≥80%) adherence and low (<80%) adherence.

Effectiveness in serodiscordant couples

In all three studies that enrolled serodiscordant couples, the HIV-infected partner was not on antiretroviral therapy. One trial enrolled few participants (n=24), and the duration of the trial was very short (4 months); no seroconversions were reported.[19] The trial by Baeten et al.[13] consisted of three arms: tenofovir/emtricitabine (n=1,568 participants), tenofovir alone (n=1,572 participants) and placebo (n=1,568 participants). Tenofovir/emtricitabine resulted in a 75% risk reduction (RR 0.25, 95% CI: 0.14 to 0.46) and tenofovir alone resulted in a 67% risk reduction (RR 0.33, 95% CI: 0.19 to 0.56). A continuation of this trial (Baeten et al. 2014[20]) compared tenofovir/emtricitabine with tenofovir alone: there was no significant difference between groups.

Effectiveness in heterosexuals

Of the five studies enrolling heterosexual participants, four were placebo-controlled and one compared different drug schedules. A meta-analysis of all placebo-controlled studies did not demonstrate a statistically significant reduction in HIV acquisition (RR 0.77, 95% CI: 0.46 to 1.29; Figure S3, Supplementary Material 4). In the only trial with high adherence (Thigpen et al.[11]), a risk reduction of 61% was noted (RR 0.39, 95% CI 0.18 to 0.83).

The efficacy results from Thigpen et al. were analysed separately by sex. Efficacy was only noted in males, with a risk reduction of 80% (RR 0.2, 95% CI 0.04 to 0.91, Supplementary Material 3.4).

A final study compared different PrEP regimens (daily PrEP, 'time-driven' PrEP and 'event-driven' PrEP).[21] Fewer infections occurred in the daily PrEP arm; however, there were no significant differences in HIV acquisition comparing either event or time-driven PrEP with daily PrEP.

Effectiveness in PWID

Only one study enrolled PWID.[9] Daily oral tenofovir was found to be effective, with a 49% reduction in HIV acquisition (RR 0.51, 95% CI: 0.29 to 0.92). In this study, HIV transmission may have occurred sexually or parenterally.

Relationship between efficacy and adherence

Efficacy was closely related to participants' adherence to PrEP across trials. A simple regression model yielded a R^2 of 0.92 ($p<0.001$) (Figure S4, Supplementary Material 4).

A meta-regression analysis was performed to account for trial size (Figure 4). Efficacy (as

RRs) and adherence (by proportion with plasma drug detectable) were strongly associated ($p<0.001$). As the proportion adherent increases from 0.5 to 0.6, the RR decreases by 0.13. Therefore, on average, a 10% decrease in adherence decreases efficacy by 13%.

Figure 4. Fitted meta-regression line of the relationship between trial-level PrEP adherence and efficacy

Figure 4 Legend: Only trials that reported plasma drug concentrations contributed to analysis, represented as circles (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), VanDamme 2012 (FEM-PrEP). The solid line represents the fitted regression line and the shaded area the 95% Confidence Interval. The X-axis represents the trial-level adherence as a proportion and the Y-axis represents the efficacy as risk ratios.

Safety

Twelve studies reported data on 'any' adverse events; ten compared PrEP with placebo and two compared tenofovir alone to tenofovir/emtricitabine. A meta-analysis of placebo-controlled trials demonstrated no significant difference between groups (RR 1.01; 95% CI 0.99 to 1.03; Figure S5, Supplementary Material 4). Comparing tenofovir with tenofovir/emtricitabine, one study noted a small increase in adverse events in the tenofovir/emtricitabine group (RR 1.23; 95% CI 1.03 to 1.33, Figure S6, Supplementary Material 4) and another failed to show any difference.

Of note, several studies reported mild decreases in renal function among PrEP users that returned to normal following discontinuation of PrEP use, while a reduction in creatinine clearance (a measure of renal function) was not observed in others.[9 13] Where renal function has been affected, PrEP was associated with mild, non-progressive and reversible reductions in creatinine clearance.[3 9 13 16 17] Some trials also found slight decreases in bone mineral

density.[11 14]

All 15 studies reported data in relation to the risk of serious adverse events: 12 were placebo-controlled, one compared PrEP with no PrEP and two compared tenofovir/emtricitabine with tenofovir. A meta-analysis of placebo-controlled trials did not find an increased risk (RR 0.91, 95% CI: 0.74 to 1.13; Figure S7, Supplementary Material 4).

In the only trial that compared PrEP with no treatment, an increased rate of serious adverse events was noted in the treatment arm (RR 3.42; 95% CI 1.4 to 8.35). However, adverse events were not considered study drug-related. Two studies compared tenofovir with tenofovir/emtricitabine: one found no significant difference between groups and another found an increased rate in the tenofovir/emtricitabine group (RR 2.48; 95% CI: 1.42 to 4.33). Of note, not all studies defined what constituted adverse events (including serious adverse events).

Fourteen studies provided data on deaths; none found an increased mortality rate associated with PrEP use, and of the deaths that occurred, none were considered to be drug-related (Figure S8, Supplementary Material 4).

Viral drug resistance mutations

Seven placebo-controlled trials provided data on HIV mutations among seroconverters. Seroconverters were subgrouped into those who had acute HIV infection at enrolment (unknown to study investigators) and seroconverters post-randomisation. In total, there were 44 seroconversions at enrolment, 25 who received study drug and 19 who received placebo. There were nine mutations detected, eight among participants receiving study drug and one in a patient receiving placebo. The RR for any drug mutation was 3.53 (95% CI:

1.18 to 10.56, Figure S9, Supplementary Material 4).

Of the nine resistance mutations at enrolment, seven were for emtricitabine. The RR for emtricitabine mutation was 3.72 (95% CI: 1.23 to 11.23) in those receiving tenofovir/emtricitabine (Figure S10, Supplementary Material 4).

Among participants who seroconverted postrandomisation, the development of resistant mutations was uncommon. Of 551 seroconverters, only seven resistance mutations were detected; one tenofovir mutation was noted in a tenofovir-only arm (k65n, a rare tenofovir resistance mutation) and six emtricitabine mutations were noted.

Risk compensation

Eleven trials measured changes in behaviour; eight measured condom use, ten measured number of sexual partners and one assessed changes in recreational drug use. Five trials assessed the change in STI rates. Due to the differences in how sexual behaviour was reported across trials, including differing definitions and at different time points, a meta-analysis was not possible.

Studies consistently showed no between-group difference in condom use or number of sexual partners. Studies showed either no overall change in condom use throughout the duration of the study (n=4 studies) or an increase in condom use (n=4 studies). Most studies showed no change in the number of sexual partners over time (n=6 studies), four studies showed a slight reduction in number of sexual partners and one showed an increase (investigators of this study noted the possibility of partner underreporting at baseline[18]). No study reported an increase in STIs or a between-group difference in STI diagnoses. In the only study to enroll intravenous drug users, a reduction in intravenous drug use, needle

sharing and number of sexual partners over the course of the study was noted.[9] Supplementary Material 3.5 presents full details of behaviour change and STI rates in individual studies.

Discussion

Summary of findings

This systematic review and meta-analysis of 25,051 individuals encompassing 38,289 person-years of follow-up data confirms that oral tenofovir-containing PrEP is both effective and safe. PrEP is particularly effective in MSM, with a risk reduction of 75% across all trials, rising to 86% in trials with high adherence. PrEP is also effective in serodiscordant couples, and no significant difference exists between single-agent tenofovir and combination tenofovir/emtricitabine.

Questions remain regarding PrEP effectiveness in other populations. One study found that PrEP was effective in PWID.[9] However, a limitation of this study is that investigators were not sure if transmission was parenteral or sexual. It is unclear if PrEP is effective in heterosexuals. PrEP was effective in preventing heterosexual HIV transmission in one trial where adherence was high (61% reduction),[11] but only in male participants. The remaining three heterosexual trials, all conducted in sub-Saharan Africa, only enrolled females and adherence was noted to be very low.[10 12 14]

Adherence varied greatly across studies, ranging from 25% to 88% by plasma drug monitoring. As expected, efficacy was found to be strongly associated with adherence ($p<0.01$), and adherence explained 92% of the variation in efficacy across trials. On average, a 10% reduction in adherence reduced efficacy by 13%.

PrEP was found to be safe. A meta-analysis of placebo-controlled trials demonstrated that adverse events (overall) and serious adverse events do not occur more commonly with PrEP compared with placebo, and no drug-related deaths were reported. There was no difference

in adverse event rates comparing single agent tenofovir with tenofovir/emtricitabine in combination. Some studies noted a transient elevation of creatinine with resolution upon discontinuation of study drug.[3 9 13 16 17] While uncommon, viral drug resistance mutations may occur in the presence of an unrecognised HIV infection at enrolment. Nine mutations were detected; eight among those receiving PrEP and one in a patient receiving placebo. Seven of these conferred resistance to emtricitabine. Development of resistance post-randomisation was uncommon.

Our findings of high effectiveness in MSM has been confirmed by two open-label extensions[23 24] that followed the conclusion of four RCTs included in this review.[3 15 17 22] One open-label extension found no seroconversions in participants that took a minimum of four pills per week.[23]

Strengths and limitations

This systematic review assessed the use of PrEP in all potentially eligible populations, and provided a GRADE assessment of important outcomes[66], ensuring a systematic and transparent approach in the development of national clinical practice guidelines for the prevention of HIV. Based on the strength of the evidence, this study informed the decision of the Irish government to implement a publicly funded PrEP programme nationally for MSM and serodiscordant couples at increased risk, and for other populations on a case-by-case basis as determined by the treating HIV specialist.

Despite the strength of the evidence, however, the present study is subject to a number of limitations. First, while PrEP is considered to have an excellent safety profile, the maximum follow-up period was 6.9 years in this review and, therefore, long-term safety was not

assessed.

Second, while risk compensation was not noted in this review, evidence from placebo-controlled trials is often insufficient to determine its presence. It is not possible to reach conclusions on the impact of PrEP on behaviour when participants do not know if they are taking active PrEP or placebo. However, it is possible to evaluate the impact of the support provided to all participants over time (provision of condoms, counselling on safer sex practices). Studies generally demonstrated no change or an improvement in safer sex practices. In the open-label PROUD study (where participants knew they were taking PrEP), there was no difference between the immediate and deferred PrEP groups in the total number of sexual partners in the three months prior to the 1-year questionnaire.[16] However, a greater proportion of the immediate group reported receptive anal sex without a condom with 10 or more partners compared with the deferred group. Importantly, there was no difference in the frequency of bacterial STIs between groups, the most reliable proxy for changes in sexual behaviour (as it is not self-reported).

Finally, the generalisability of studies to other clinical settings should be done with caution. All trials that enrolled heterosexuals were conducted in sub-Saharan Africa, a part of the world with a generalised HIV epidemic and suboptimal antiretroviral coverage. Additionally, the only trial that enrolled PWID was conducted in Bangkok, where needle exchange was unavailable to participants, and investigators could not differentiate sexually from parenterally acquired HIV.

Research in context and implications for practice

Most recent systematic reviews focussed solely on the MSM population[25 26], and are in

agreement with our findings for this group. To our knowledge, this systematic review provides the first GRADE assessment of the totality of evidence across all populations that includes more recent trials with high adherence.[16 17] Our GRADE assessment differs significantly from that of Okwundu et al., published in 2012.[27]

Our quantification of the strength of the association between adherence and efficacy through meta-regression highlights the clinical importance of medication adherence support and counselling to prospective PrEP users. Additionally, our finding of emtricitabine resistance mutations occurring almost four times more often in those with acute HIV enrolment has implications for PrEP implementation going forward. Assessing if the patient could be in the 'window period' (the time between exposure to HIV and the point when HIV testing will give an accurate result) at enrolment is of critical importance, to ensure the patient is HIV negative prior to commencing PrEP. This highlights the need for PrEP delivery as part of a monitored programme that incorporates HIV testing and patient counselling on the risk and long-term consequences of resistance if poorly adherent to PrEP.

An additional finding of interest is the lack of significant difference in the effectiveness and safety of single agent tenofovir compared with combined tenofovir/emtricitabine. This may have implications for clinical practice, as tenofovir may be a suitable alternative for emtricitabine-allergic patients, and in resource-poor settings if cost or procurement of combination tenofovir/emtricitabine is an issue.

Conclusions

In conclusion, high-certainty evidence exists that PrEP is safe and, assuming adequate adherence, effectively prevents HIV in MSM and serodiscordant couples. One study found

PrEP to be effective in PWID. The uncertainty regarding PrEP effectiveness in heterosexual individuals persists. Clinicians and policy-makers may decide to recommend PrEP to heterosexual individuals on a case-by-case basis, acknowledging adherence-related issues reported in trials. This review emphasises the importance of adherence support to ensure PrEP effectiveness is maintained, as well as the need for frequent HIV testing at enrolment and follow-up to avoid viral drug resistance mutations. Following the conclusion of this study, the Irish government implemented a publicly-funded PrEP programme for all individuals at increased risk of HIV acquisition, and developed national clinical practice guidelines for the provision of PrEP.

Author contributions: Dr. O Murchu: concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of paper for important intellectual content, statistical analysis. Dr. Marshall: acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of paper for important intellectual content. Dr. Teljeur: concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of paper for important intellectual content, statistical analysis, supervision. Dr. Hayes: concept and design, drafting of the manuscript, supervision. Dr. Harrington: concept and design, critical revision of paper for important intellectual content, analysis and interpretation of data, drafting of the manuscript, supervision. Dr. Moran: concept and design, drafting of the manuscript, supervision. Dr. Ryan: concept and design, critical revision of paper for important intellectual content, drafting of the manuscript, supervision.

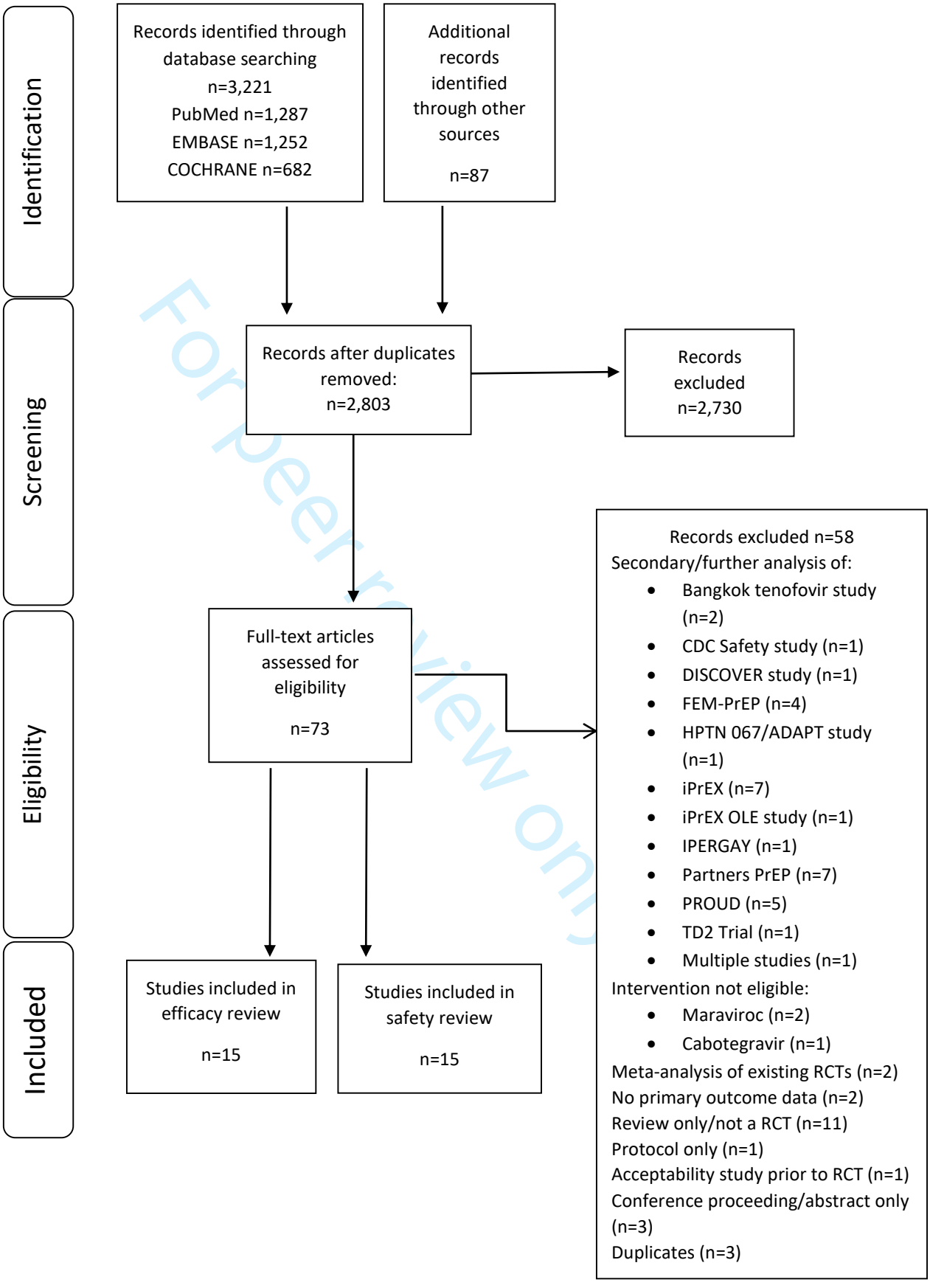
Acknowledgements: Dr Fiona Lyons, Clinical Lead in Sexual Health; the HSE's Sexual Health and Crisis Pregnancy Programme; the Gay Men's Health Centre Dublin; HIV Ireland; Act Up Dublin; and the Gay Health Network.

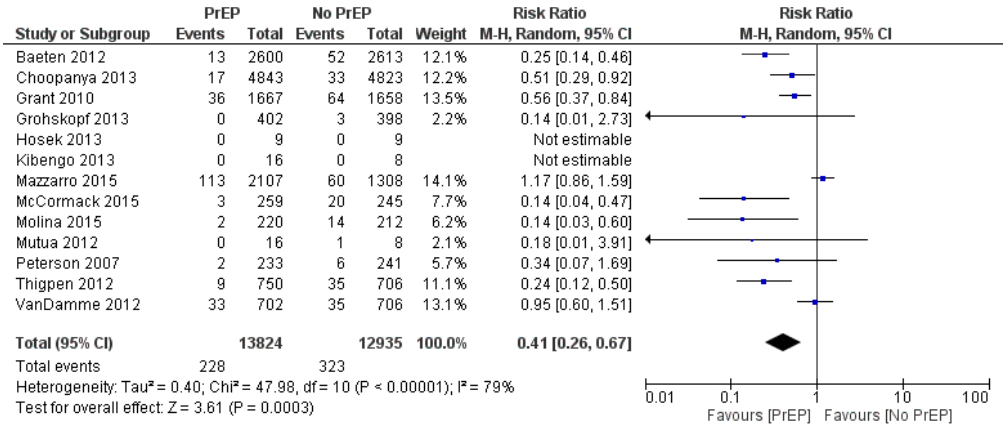
References

1. UNAIDS. Global HIV & AIDS statistics — 2019 fact sheet. Available at: https://www.unaids.org/en/resources/fact-sheet. Accessed 22.7.2019.
2. WHO. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations, 2014. Available at: https://www.who.int/hiv/pub/guidelines/keypopulations/en/. Accessed 22.7.2019.
3. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. 2010; 363(27).
4. WHO. WHO Expands Recommendation On Oral Preexposure Prophylaxis Of Hiv Infection (Prep), 2015. Available at: https://apps.who.int/iris/bitstream/handle/10665/197906/WHO_HIV_2015.48_eng.pdf;jsessionid=7B04813AFDE92D7F5EE3D71C8E921BBA?sequence=1. Accessed 22.7.2019.
5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339 doi: 10.1136/bmj.b2700
6. GRADE. The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) working group. Available at: http://www.gradeworkinggroup.org/. Accessed 22.7.2019.
7. Cochrane. The Cochrane Risk of Bias tool. Cochrane Handbook: Chapter 8. Available at: https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm.
8. Guenhan BK. MetaStan: Bayesian Meta-Analysis via 'Stan', R package version 0.2.0. Available at: https://CRAN.R-project.org/package=MetaStan.
9. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England)* 2013;381(9883):2083-90. doi: 10.1016/s0140-6736(13)61127-7
10. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *The New England journal of medicine* 2012;367(5):411-22. doi: 10.1056/NEJMoa1202614
11. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *New England journal of medicine* 2012; 367(5).
12. Peterson L, Taylor D, Roddy R, et al. Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial. *PLoS Clinical Trials* 2007;2(5):e27. doi: 10.1371/journal.pctr.0020027
13. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *New England journal of medicine* 2012; 367(5).
14. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *The New England journal of medicine* 2015;372(6):509-18. doi: 10.1056/NEJMoa1402269
15. Grohskopf LA, Chillag KL, Gvetadze R, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *Journal of acquired immune deficiency syndromes (1999)* 2013;64(1):79-86. doi: 10.1097/QAI.0b013e31828ece33
16. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet (London, England)* 2016;387(10013):53-60. doi: 10.1016/s0140-6736(15)00056-2

17. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *The New England journal of medicine* 2015;373(23):2237-46.
18. Mutua G, Sanders E, Mugo P, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. *Plos one* 2012; 7(4).
19. Kibengo FM, Ruzagira E, Katende D, et al. Safety, adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. *PLoS One* 2013;8(9):e74314. doi: 10.1371/journal.pone.0074314
20. Baeten JM, Donnell D, Mugo NR, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. *The lancet Infectious diseases* 2014; 14(11).
21. Bekker LG, Roux S, Sebastien E, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. *The lancet HIV* 2018;5(2):e68-e78. doi: 10.1016/s2352-3018(17)30156-x
22. Hosek SG, Siberry G, Bell M, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. *Journal of acquired immune deficiency syndromes (1999)* 2013;62(4):447-56.
23. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014;14(9):820-9. doi: 10.1016/s1473-3099(14)70847-3
24. Molina JM CI, Spire B, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV 2017; 4: e402–e410. 2017
25. Huang X, Hou J, Song A, et al. Efficacy and Safety of Oral TDF-Based Pre-exposure Prophylaxis for Men Who Have Sex With Men: A Systematic Review and Meta-Analysis. *Frontiers in pharmacology* 2018;9:799. doi: 10.3389/fphar.2018.00799
26. Freeborn K, Portillo CJ. Does pre-exposure prophylaxis for HIV prevention in men who have sex with men change risk behaviour? A systematic review. *J Clin Nurs* 2018;27(17-18):3254-65. doi: 10.1111/jocn.13990
27. Okwundu CI, Uthman OA, Okoromah CAN. Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. *Cochrane Database of Systematic Reviews* 2012(7) doi: 10.1002/14651858.CD007189.pub3

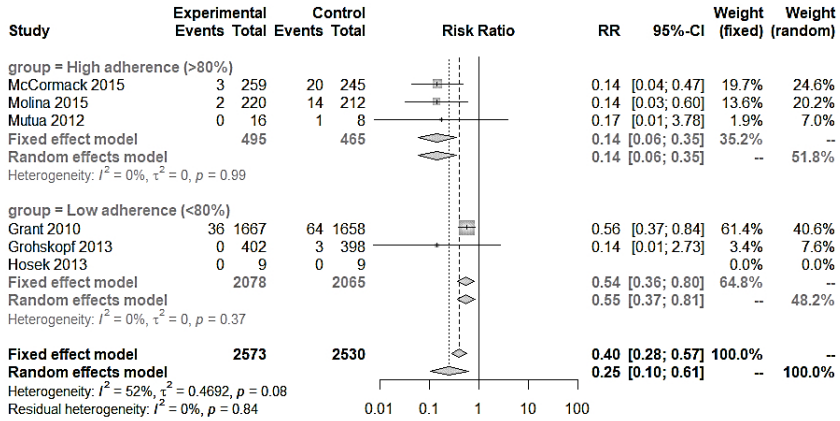
Figure 1. **PRISMA diagram of study selection**



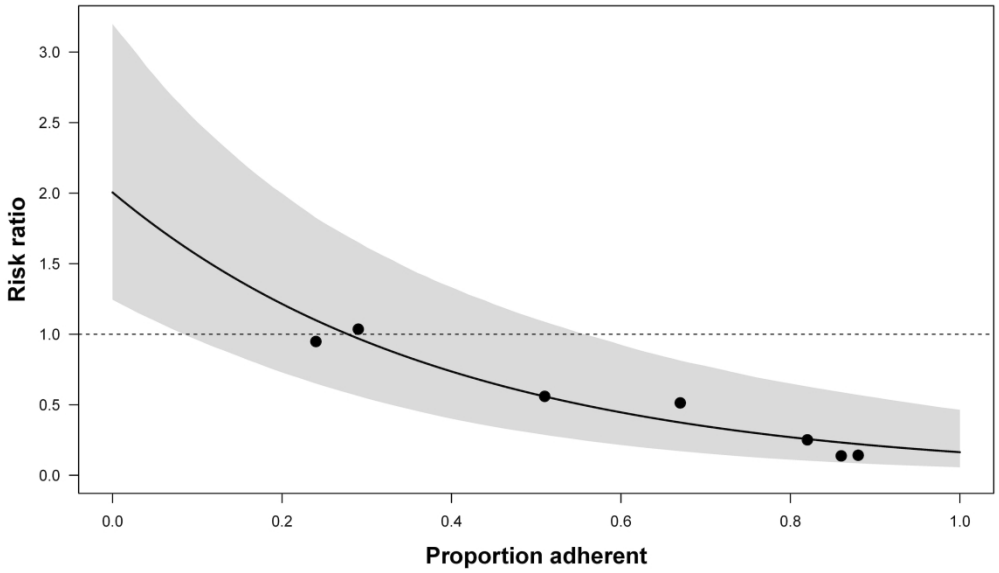


Forest plot of the meta-analysis of HIV incidence in all trials, PrEP versus placebo or no drug

274x118mm (72 x 72 DPI)



Forest plot of the meta-analysis of HIV incidence in all MSM trials, PrEP versus placebo or no drug. Subgroups include high (≥80%) adherence and low (<80%) adherence.



Only trials that reported plasma drug concentrations contributed to analysis, represented as circles (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), VanDamme 2012 (FEM-PrEP). The solid line represents the fitted regression line and the shaded area the 95% Confidence Interval. The X-axis represents the trial-level adherence as a proportion and the Y-axis represents the efficacy as risk ratios.

275x159mm (300 x 300 DPI)

Supplementary Material

Supplementary Material 1: Protocol

Supplementary Material 2: Methods

Supplementary Material 3: Results

Supplementary Material 4: Additional figures and forest plots

Supplementary Material 1: Systematic Review Protocol

PROSPERO entry: CRD42017065937

Clinical effectiveness, safety, adherence and changes in sexual behaviour associated with pre-exposure prophylaxis (PrEP) for the prevention of HIV in all populations

Eamon O Murchu

Citation

Eamon O Murchu. Clinical effectiveness, safety, adherence and changes in sexual behaviour associated with pre-exposure prophylaxis (PrEP) for the prevention of HIV in all populations. PROSPERO 2017 CRD42017065937 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017065937

Review question

What is the clinical effectiveness of pre-exposure prophylaxis for the prevention of HIV, overall and by mode of transmission?
How does adherence affect these estimates?
Is PrEP safe?
Is there trial evidence to suggest a change in sexual behaviour associated with PrEP?

Searches

The following databases will be searched: MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL).
Restrictions:
Language: English.
Date: all articles published to present.
Human studies only.

Types of study to be included

Randomised clinical trials.

Condition or domain being studied

In collaboration with Trinity College Dublin and the Sexual Health and Crisis Pregnancy Programme, this systematic review will inform health policy in Ireland.

Participants/population

All, including MSM transmission (males who have sex with males), transmission between serodiscordant sexual partners, heterosexual transmission, and injection drug use.

Intervention(s), exposure(s)

Administration of any tenofovir-based pre-exposure prophylaxis.

Comparator(s)/control

No PrEP.

Main outcome(s)

HIV acquisition in the intervention and control arms of RCTs.

** Measures of effect*

RRs.

Additional outcome(s)

Adverse events associated with PrEP;
Behaviour change;
STI transmission;
Adherence.

** Measures of effect*

RRs.

Data extraction (selection and coding)

Two researchers will independently extract data from studies which meet the inclusion criteria. Any discrepencies between the researchers will be resolved by discussion with a third independent researcher.

Risk of bias (quality) assessment

The Cochrane risk of bias tool will be used to assess risk of bias in the RCTs.

Strategy for data synthesis

A quantitative analysis of the extracted data, and a meta-analysis of the clinical effectiveness of PrEP will be performed. A meta-regression will be performed to measure the association between adherence and efficacy.

Analysis of subgroups or subsets

Subgroup analyses will include:
Dosing schedule (daily, episodic and periodic);
Risk group (4 risk group categories identified).

Contact details for further information

Dr Eamon O Murchu
eomurchu@hiqa.ie

Organisational affiliation of the review

Health Information and Quality Authority; University of Dublin, Trinity College
www.hiqa.ie

Review team members and their organisational affiliations

Dr Eamon O Murchu. Health Information and Quality Authority, Trinity College Dublin

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

15 June 2017

Anticipated completion date

30 August 2019

Funding sources/sponsors

None

Conflicts of interest

None known

Language

English

Country

Ireland

Stage of review

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Anti-HIV Agents; Cost-Benefit Analysis; Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination; HIV; HIV Infections; Homosexuality, Male; Humans; Male; Pre-Exposure Prophylaxis; Primary Prevention; Treatment Outcome

Date of registration in PROSPERO

12 May 2017

Date of first submission

12 July 2019

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Supplementary Material

Detailed protocol:

1. Background

Human Immunodeficiency Virus (HIV) persists as a significant public health threat. There were 511 HIV notifications in Ireland in 2016, giving a rate of 11.2 per 100,000. This is the highest rate ever reported in Ireland.[1] Males who have sex with males (MSM) remain the population most affected by HIV. In 2015, there were 247 new HIV diagnoses reported among MSM, just over half (51%) of all diagnoses in 2015. The number of diagnoses in 2015 was the highest number ever reported among MSM in Ireland and represents an increase of 34% compared to 2014.[1]

Pre-exposure prophylaxis (PrEP) is a biomedical HIV prevention strategy whereby oral anti-retrovirals (namely tenofovir-emtricitabine, Truvada®) are taken daily by HIV-negative individuals to prevent infection. In their latest guidelines, the World Health Organization (WHO) recommends that PrEP containing tenofovir disoproxil fumarate should be offered as part of HIV prevention programmes to people at 'substantial risk of HIV infection'.[2] Of note, PrEP offers no protection against sexually transmitted infections other than HIV.

In August 2016, the European Commission granted marketing authorisation for once-daily Truvada® in combination with safer-sex practices to reduce the risk of sexually acquired HIV-1 infection among uninfected adults at high risk. Therefore Truvada® is licensed for PrEP in Ireland. However, it has not been made available through the Health Service Executive (HSE); no PrEP programme has been implemented and it is not reimbursed through the Primary Care Reimbursement Scheme.

Elsewhere, in the US the FDA has approved Truvada® for PrEP since 2012.[3] In April 2017, Scotland became the first EU country to announce it would publicly fund PrEP.[4] In France, Truvada® is publicly funded under an "emergency Recommendation of Temporary Use (RTU) measure", since January 2016.[5]

2. Objective

To perform a systematic review of the efficacy of oral antiretroviral pre-exposure prophylaxis (PrEP) therapy to prevent HIV infection in all populations.

3. Methods

A systematic review of Randomised Controlled Trials (RCTs) will be performed. Systematic review will be registered with PROSPERO.

3.1 Criteria for considering studies for this review

Types of studies

RCTs that evaluated the efficacy of antiretroviral chemoprophylaxis in preventing HIV infection in men who have sex with men (MSM).

Types of participants

All populations at increased risk, including MSM transmission (males who have sex with males), transmission between serodiscordant sexual partners, heterosexual transmission, and people who inject drugs.

Types of interventions

Trials comparing various types of oral PrEP regimens:

- Tenofovir only versus placebo or no treatment
- Tenofovir + Emtricitabine versus placebo or no treatment
- Tenofovir only versus Tenofovir + Emtricitabine
- Any other oral PrEP regimen versus placebo or no treatment.

Types of outcome measures

Primary outcome:

Incidence of new HIV infections.

Secondary outcomes:

1. Adherence to PrEP (as measured by the primary studies)
2. Adverse events associated with PrEP (frequency and type of adverse effects or complications)
3. New STI infections
4. Behaviour change associated with PrEP administration (number of episodes of condomless anal intercourse and number of new sexual partners).

Supplementary Material

Figure 1 outlines the PICOS criteria for inclusion of studies for inclusion.

Table S1.1: PICOS criteria

PICOS Criteria: Study Selection	
Population	Males who have sex with males, heterosexuals at increased risk, serodiscordant couples, people who inject drugs
Intervention	Pre-exposure prophylaxis (any oral antiretroviral formulation)
Comparator	Placebo or no treatment
Outcomes	**Primary outcome:** HIV incidence **Secondary outcomes:** 1. Adherence to PrEP (as measured by the primary studies) 2. Adverse events associated with PrEP (frequency and type of adverse effects or complications) 3. New STI infections 4. Behaviour change reported in RCTs associated with PrEP administration (episodes of condomless anal intercourse and number of new sexual partners)
Studies	Randomised Controlled Trials

3.2 Search methods for identification of studies

Electronic searches

Electronic searches will be conducted in Medline (PubMed), Embase and the Cochrane Register of Controlled Trials. Additional searches will include the CRD DARE Database, Morbidity and Mortality Weekly Report (CDC), Eurosurveillance reports and hand-searching of journals.

The WHO International Clinical Trials Registry Platform and ClinicalTrials.gov will be searched for ongoing or prospective trials.

No restrictions will be placed based on location of the intervention. No language restrictions will be used. Articles in languages other than English will be translated where necessary.

The detailed search strategies for each of the databases MEDLINE via PubMed, EMBASE and The Cochrane Central Register of Controlled Trials are as follows:

Searching other resources

Hand searches of the reference lists of all included studies will be performed.

3.3 Data collection

Two reviewers will independently read the titles, abstracts, and descriptor terms of the search output from the different databases to identify potentially eligible studies. Full text articles will be obtained for all citations identified as potentially eligible. Both reviewers will independently inspect these to establish the relevance of the articles according to the pre-specified criteria. Studies will be reviewed for relevance based on study design, types of participants, interventions, and outcome measures. Reasons for excluding potentially relevant studies will be provided in an excluded studies table.

3.4 Data extraction and management

Data will be independently extracted using an agreed pro forma. Both reviewers will verify the extracted data. Extracted information will include the following:

- Study details: citation, study design and setting, time period and source of funding.
- Participant details: study population demographics, risk characteristics, population size and attrition rate.
- Intervention details: type of drug, comparator, dose, duration and route of administration.
- Outcome details: incidence of HIV infection (including type of laboratory tests used to confirm HIV diagnosis before and after administering PrEP), degree of adherence to PrEP, adverse effects, other STI infections.

RevMan software will be used to record extracted data. The reviewers will independently extract the data and enter them into RevMan; all entries will be rechecked by both reviewers, and all disagreements will be resolved by discussion. If results are pooled, a random effects meta-analysis, using the Mantel-Haenzel odds ratio, will be employed. Table 4 summarises the data collection, management and analysis.

Table S1.2: Data Collection, Management & Analysis

Data Collection and Management	
Selection of studies	• Citations will be screened by one reviewer to eliminate clearly irrelevant studies • Two people will independently review the remaining citations per the inclusion criteria • Any disagreements will be resolved by discussion, or if necessary a third reviewer
Data extraction and management	• Data extraction will be performed independently onto a data extraction pro forma by two people • Any disagreements will be resolved by discussion or a third reviewer • RevMan software will be used to record extracted data
Assessment of risk of bias in included studies	• Risk of bias will be assessed using the Cochrane Risk of Bias Tool for RCTs • This will be performed by two people independently, with any disagreement being resolved by discussion or a third party • Small study bias will be assessed using a funnel plot and Egger's test • An overall assessment of the quality of the evidence will be assessed using the GRADE approach†
Measures of treatment effect and data synthesis	• Effect sizes will be expressed as the reduction in relative risk (RR) of HIV infection in the treatment group compared to control • A meta-analysis will be performed to provide a pooled risk if there is sufficient homogeneity across studies (all statistical analysis will be performed in STATA® SE) • If significant heterogeneity is observed, a narrative metasynthesis will be performed.
Assessment of heterogeneity	• Clinical heterogeneity will be assessed by the reviewers based on the description of the interventions in the RCTs • Statistical heterogeneity will be examined using the I^2 statistic.

†The Cochrane Handbook. Section 12.2.1: The GRADE approach. Available at: http://handbook.cochrane.org/chapter_12/12_2_1_the_grade_approach.htm. Accessed May 2017.

3.5 Assessment of risk of bias in included studies

Two reviewers will independently examine the components of each included trial for risk of bias using a standard form. The Cochrane Risk of Bias tool will be employed. This will include information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the studies will be assessed and classified as adequate, inadequate or unclear as per the Cochrane Handbook of Systematic Reviews of Interventions. Where differences arise, they will be resolved by discussions with the third reviewer.

Table 5 outlines the potential risks of bias that will be assessed in included studies.

Table S1.3:: Risk of Bias

Risk of Bias	
Sequence generation	• Adequate: investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelope shuffling, etc. • Inadequate: investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number. • Unclear: insufficient information to permit judgement of the sequence generation process.
Allocation concealment	• Adequate: participants and the investigators enrolling participants cannot foresee assignment (e.g. central allocation; or sequentially numbered, opaque, sealed envelopes). • Inadequate: participants and investigators enrolling participants can foresee upcoming assignment (e.g. an open random allocation schedule (e.g. a list of random numbers); or envelopes were unsealed or nonopaque or not sequentially numbered). • Unclear: insufficient information to permit judgement of the allocation concealment or the method not described
Blinding	• Adequate: blinding of the participants, key study personnel and outcome assessor, and unlikely that the blinding could have been broken. Or lack of blinding unlikely to introduce bias. No blinding in the situation where non-blinding is not likely to introduce bias.

	• Inadequate: no blinding, incomplete blinding and the outcome is likely to be influenced by lack of blinding. • Unclear: insufficient information to permit judgement of adequacy or otherwise of the blinding.
Incomplete outcome data	• Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups. • Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data. • Unclear: insufficient reporting of attrition or exclusions.
Selective Reporting	• Adequate: a protocol is available which clearly states the primary outcome as the same as in the final trial report. • Inadequate: the primary outcome differs between the protocol and final trial report. • Unclear: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.
Other sources of bias	• Adequate: there is no evidence of bias from other sources. • Inadequate: there is potential bias present from other sources (e.g. early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design).

An overall assessment of the quality of the evidence will be assessed using the GRADE approach (the Cochrane Handbook, Section 12.2.1: The GRADE approach).

3.6 Measures of treatment effect

Outcome measures for dichotomous data (e.g., HIV infection) will be calculated as a relative risk (RR) with 95% confidence intervals (CI). A meta-analysis will be performed to provide a pooled risk if there is sufficient homogeneity across studies (all statistical analysis will be performed in Review Manager and R).

3.7 Dealing with missing data

Study authors will be contacted to provide further information on the results.

3.8 Assessment of heterogeneity

Clinical heterogeneity will be assessed by the reviewers based on the description of the interventions in the RCTs. Statistical heterogeneity will be examined using the I^2 statistic.

3.9 Subgroup analysis

Subgroup analyses will subsequently be performed. Firstly, subgroup analysis by risk of HIV infection will be analysed. The presence of any of the following in the prior 12 month period will indicate a substantially higher risk of infection: use of illicit drugs during sex ('chemsex'), anal STI diagnosis or treatment with post-exposure prophylaxis. These risk factors are commonly assessed in trials.[6 7]

Secondly, differing dosing schedules will be investigated. While its only licensed indication is daily administration, alternative schedules have been examined in RCTs, such as "on-demand" PrEP during high-risk periods.[7]

Finally, adherence will be assessed. Clinical effectiveness will be estimated when excluding participants with poor adherence, either through plasma drug concentration monitoring or self-report.

3.10 Reporting guidelines

Reporting will adhere to the PRISMA guidelines for systematic reviews.[8]

References

1. Jain A, van Hoek AJ, Boccia D, et al. Lower vaccine uptake amongst older individuals living alone: A systematic review and meta-analysis of social determinants of vaccine uptake. *Vaccine* 2017;35(18):2315-28. doi: 10.1016/j.vaccine.2017.03.013
2. WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015. Available at: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf. Accessed May 2017.
3. Wong VW, Lok KY, Tarrant M. Interventions to increase the uptake of seasonal influenza vaccination among pregnant women: A systematic review. *Vaccine* 2016;34(1):20-32. doi: 10.1016/j.vaccine.2015.11.020
4. Bisset KA, Paterson P. Strategies for increasing uptake of vaccination in pregnancy in high-income countries: A systematic review. *Vaccine* 2018;36(20):2751-59. doi: 10.1016/j.vaccine.2018.04.013

5. Kang GJ, Culp RK, Abbas KM. Facilitators and barriers of parental attitudes and beliefs toward school-located influenza vaccination in the United States: Systematic review. *Vaccine* 2017;35(16):1987-95. doi: 10.1016/j.vaccine.2017.03.014
6. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet (London, England)* 2016;387(10013):53-60. doi: 10.1016/s0140-6736(15)00056-2 [published Online First: 2015/09/14]
7. Molina J-M, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *New England Journal of Medicine* 2015;373(23):2237-46. doi: doi:10.1056/NEJMoa1506273
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339 doi: 10.1136/bmj.b2700

Supplementary Material 2: Methods

2.1 Database search

2.2 Data collection, management and analysis

S2.1

Database search

Table S2.1.1 PubMed

Search	Most Recent Queries
#6	Search #1 AND #2 AND #5
#5	Search #3 OR #4
#4	Search tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil
#3	Search pre-exposure prophylaxis[tiab] OR preexposure prophylaxis[tiab] OR PREP[tiab] OR anti-retroviral chemoprophylaxis[tiab] OR antiretroviral chemoprophylaxis[tiab] OR chemoprevention[mh] OR chemoprevention[tiab] OR HIV prophylaxis[tiab]
#2	Search (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR HIV[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR HIV infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]

Table S2.1.2. Cochrane Central register

ID	Search
#1	MeSH descriptor HIV Infections explode all trees
#2	MeSH descriptor HIV explode all trees
#3	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME
#4	MeSH descriptor Sexually Transmitted Diseases, Viral, this term only
#5	(#1 OR #2 OR #3 OR #4)
#6	MeSH descriptor Chemoprevention explode all trees
#7	pre-exposure prophylaxis:ti,ab,kw OR preexposure prophylaxis:ti,ab,w OR PREP:ti,ab,kw OR anti-retroviral chemoprophylaxis:ti,ab,kw OR antiretroviral chemoprophylaxis:ti,ab,kw OR hiv prophylaxis:ti,ab,kw
#8	(#6 OR #7)
#9	tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil
#10	(#8 OR #9)
#11	(#5 AND #10)

Table S2.1.3. Embase

No.	Query
#6	#1 AND #2 AND #5
#5	#3 OR #4

Supplementary Material

#4	'tenofovir'/syn OR tnf OR Tenofovir OR 'pmpa'/syn OR 'viread'/syn OR 'emtricitabine'/syn OR emc OR 'truvada'/syn OR 'emtriva'/syn OR 'coviracil'/syn
#3	'pre-exposure prophylaxis' OR 'preexposure prophylaxis' OR prep OR 'anti-retroviral chemoprophylaxis' OR 'antiretroviral chemoprophylaxis' OR 'chemoprevention'/syn OR 'hiv prophylaxis' OR 'chemoprophylaxis'/syn
#2	random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over*:ti OR cross?over:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/de OR 'crossover procedure' OR 'double-blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/de OR 'single-blind procedure' OR 'randomised controlled trial'/de OR 'randomised controlled trial' OR allocat*:ti OR allocat*:ab
#1	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection'/de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus'/de OR 'human immunodeficiency virus' OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab OR 'human immunedeficiency virus':ti OR 'human immunedeficiency virus':ab OR 'human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab OR 'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab OR 'acquired immunedeficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab

S2.2

Table S2.2.1: Data collection, management and analysis

Data collection and management	
Selection of studies	Citations will be screened by one reviewer to eliminate clearly irrelevant studies. Two people will independently review the remaining citations per the inclusion criteria. Any disagreements will be resolved by discussion or, if necessary, a third reviewer.
Data extraction and management	Data extraction will be performed independently onto a data extraction pro forma by two people. Any disagreements will be resolved by discussion or a third reviewer. RevMan software will be used to record extracted data.
Assessment of risk of bias in included studies	Risk of bias will be assessed using the Cochrane Risk of Bias Tool for randomised control trails (RCTs). This will be performed by two people independently, with any disagreement being resolved by discussion or a third party. Small study bias will be assessed using a funnel plot and Egger's test. An overall assessment of the quality of the evidence will be assessed using the GRADE approach.†
Measures of treatment effect and data synthesis	Effect sizes will be expressed as the reduction in relative risk (RR) of HIV infection in the treatment group compared to control. A meta-analysis will be performed to provide a pooled risk if there is sufficient homogeneity across studies (all statistical analysis will be performed in Review Manager 5.3 software). If significant heterogeneity is observed, a narrative metasynthesis will be performed.
Assessment of heterogeneity	Clinical heterogeneity will be assessed by the reviewers based on the description of the interventions in the RCTs. Statistical heterogeneity will be examined using the I^2 statistic. I^2 values above 50–70% will be deemed heterogenous.

†The Cochrane Handbook. Section 12.2.1: The GRADE approach. Available at:

http://handbook.cochrane.org/chapter_12/12_2_1_the_grade_approach.htm. Accessed May 2017.

Supplementary Material 3: Results

3.1 List of included/excluded studies

3.2 Risk of Bias assessment

3.3 Adherence

3.4 Results from Thigpen 2012 (by gender)

3.5 Change in sexual behaviour/STI rates

S3.1

List of studies included in review

1. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. New England journal of medicine [Internet]. 2012; 367(5):[399-410 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/266/CN-00840266/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770474/pdf/nihms493581.pdf.

2. Baeten JM, Heffron R, Kidoguchi L, Mugo NR, Katabira E, Bukusi EA, et al. Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1–serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda. PLOS Medicine. 2016;13(8):e1002099.

3. Bekker LG, Roux S, Sebastien E, Yola N, Amico KR, Hughes JP, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. The lancet HIV. 2018;5(2):e68-e78.

4. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet (London, England). 2013;381(9883):2083-90.

5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New England journal of medicine [Internet]. 2010; 363(27):[2587-99 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/306/CN-00771306/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079639/pdf/nihms264954.pdf.

6. Grohskopf LA, Chillag KL, Gvetadze R, Liu AY, Thompson M, Mayer KH, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. Journal of acquired immune deficiency syndromes (1999). 2013;64(1):79-86.

7. Hosek SG, Siberry G, Bell M, Lally M, Kapogiannis B, Green K, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. Journal of acquired immune deficiency syndromes (1999). 2013;62(4):447-56.

8. Kibengo FM, Ruzagira E, Katende D, Bwanika AN, Bahemuka U, Haberer JE, et al. Safety,

adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. PLoS One. 2013;8(9):e74314.

9. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2015;372(6):509-18.

10. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet (London, England). 2016;387(10013):53-60.

11. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. The New England journal of medicine. 2015;373(23):2237-46.

12. Mutua G, Sanders E, Mugo P, Anzala O, Haberer JE, Bangsberg D, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. Plos one [Internet]. 2012; 7(4):[e33103 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/614/CN-00848614/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325227/pdf/pone.0033103.pdf.

13. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial. PLoS Clinical Trials. 2007;2(5):e27.

14. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. New England journal of medicine [Internet]. 2012; 367(5):[423-34 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/265/CN-00840265/frame.html.

15. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2012;367(5):411-22.

Supplementary Material

List of studies excluded from review

1. Agot K, Taylor D, Corneli AL, Wang M, Ambia J, Kashuba AD, et al. Accuracy of Self-Report and Pill-Count Measures of Adherence in the FEM-PrEP Clinical Trial: Implications for Future HIV-Prevention Trials. AIDS and behavior. 2015;19(5):743-51. [reason: secondary analysis of FEM-PrEP]

2. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Science translational medicine. 2012;4(151):151ra25. [reason: secondary analysis of iPrEX]

3. Baeten JM, Donnell D, Mugo NR, Ndase P, Thomas KK, Campbell JD, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. The lancet Infectious diseases [Internet]. 2014; 14(11):[1055-64 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/639/CN-01053639/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252589/pdf/nihms635147.pdf. [reason: duplicate]

4. Buchbinder SP, Glidden DV, Liu AY, McMahan V, Guanira JV, Mayer KH, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. The Lancet Infectious diseases. 2014;14(6):468-75. [reason: secondary analysis of iPrEX]

5. Buchbinder SP, Liu AY. CROI 2014: New tools to track the epidemic and prevent HIV infections. Topics in Antiviral Medicine. 2014;22(2):579-93. [reason: review; not a RCT]

6. Campbell JD, Herbst JH, Koppenhaver RT, Smith DK. Antiretroviral prophylaxis for sexual and injection drug use acquisition of HIV. American Journal of Preventive Medicine. 2013;44(1 SUPPL. 2):S63-S9. [reason: review, not a RCT]

7. Celum C, Baeten JM. Antiretroviral-based HIV-1 prevention: Antiretroviral treatment and pre-exposure prophylaxis. Antiviral Therapy. 2012;17(8):1483-93. [reason: review/not a RCT]

8. Corneli AL, Deese J, Wang M, Taylor D, Ahmed K, Agot K, et al. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. Journal of acquired immune deficiency syndromes (1999). 2014;66(3):324-31. [reason: secondary analysis of FEM-PrEP]

9. Corneli AL, McKenna K, Headley J, Ahmed K, Odhiambo J, Skhosana J, et al. A descriptive analysis of perceptions of HIV risk and worry about acquiring HIV among FEM-PrEP

participants who seroconverted in Bondo, Kenya, and Pretoria, South Africa. Journal of the International AIDS Society. 2014;17(3). [reason: secondary analysis of FEM-PrEP]

10. Deutsch MB, Glidden DV, Sevelius J, Keatley J, McMahan V, Guanira J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. The lancet HIV. 2015;2(12):e512-9. [reason: secondary analysis of iPrEX]

11. Dolling DI, Desai M, McOwan A, Gilson R, Clarke A, Fisher M, et al. An analysis of baseline data from the PROUD study: An open-label randomised trial of pre-exposure prophylaxis. Trials. 2016;17(1). [reason: secondary analysis of PROUD]

12. Dunn DT, Glidden DV. Statistical issues in trials of preexposure prophylaxis. Current Opinion in HIV and AIDS. 2016;11(1):116-21. [reason: review/not a RCT]

13. Elbirt D, Mahlab-Guri K, Bezalel-Rosenberg S, Asher I, Sthoeger Z. Pre-exposure prophylaxis as a method for prevention of human immunodeficiency virus infection. Israel Medical Association Journal. 2016;18(5):294-8. [reason: review, not a RCT]

14. Fidler S, Bock P. Prophylactic antiretroviral HIV therapy prevents infection in heterosexual men and women. Evidence-Based Medicine. 2013;18(5):184-5. [Reason: not a RCT, review of Baeten et al.]

15. Gilmore HJ, Liu A, Koester KA, Amico KR, McMahan V, Goicochea P, et al. Participant experiences and facilitators and barriers to pill use among men who have sex with men in the iPrEx pre-exposure prophylaxis trial in San Francisco. AIDS patient care and stds [Internet]. 2013; 27(10):[560-6 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/551/CN-00962551/frame.html. [reason: secondary analysis of iPrEX]

16. Grangeiro A, Couto MT, Peres MF, Luiz O, Zucchi EM, de Castilho EA, et al. Pre-exposure and postexposure prophylaxes and the combination HIV prevention methods (The Combine! Study): protocol for a pragmatic clinical trial at public healthcare clinics in Brazil. BMJ open. 2015;5(8):e009021. [reason: protocol]

17. Grant RM, Liegler T, Defechereux P, Kashuba AD, Taylor D, Abdel-Mohsen M, et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women. AIDS (London, England). 2015;29(3):331-7. [reason: not an efficacy RCT; further analysis of FEM-PrEP]

18. Gray RH, Wawer MJ. Infection in 2012: Mixed results of pre-exposure prophylaxis for HIV prevention. Nature Reviews Urology. 2013;10(2):74-5. [reason: review]

19. Gulick RM, Wilkin TJ, Chen YQ, Landovitz RJ, Amico KR, Young AM, et al. Phase 2 Study of the Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV

Infection in Men Who Have Sex With Men (HPTN 069/ACTG A5305). The Journal of infectious diseases. 2017;215(2):238-46. [reason: different intervention (maraviroc)]

20. Gulick RM, Wilkin TJ, Chen YQ, Landovitz RJ, Amico KR, Young AM, et al. Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV Infection in Women: A Phase 2 Randomized Trial. Annals of internal medicine. 2017;167(6):384-93. [reason: different intervention (maraviroc)]

21. Gust DA, Soud F, Hardnett FP, Malotte CK, Rose C, Kebaabetswe P, et al. Evaluation of Sexual Risk Behavior Among Study Participants in the TENOFOVIR2 PrEP Study Among Heterosexual Adults in Botswana. Journal of acquired immune deficiency syndromes (1999). 2016;73(5):556-63. [reason: secondary analysis of TD2 trial]

22. Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, et al. Adherence to Antiretroviral Prophylaxis for HIV Prevention: A Substudy Cohort within a Clinical Trial of serodiscordant Couples in East Africa. PLoS Medicine. 2013;10(9). [reason: secondary analysis of Partners PrEP]

23. Hanscom B, Janes HE, Guarino PD, Huang Y, Brown ER, Chen YQ, et al. Brief report: Preventing HIV-1 infection in women using oral preexposure prophylaxis: A meta-analysis of current evidence. Journal of Acquired Immune Deficiency Syndromes. 2016;73(5):606-8. [reason: meta-analysis of RCTs]

24. Jiang J, Yang X, Ye L, Zhou B, Ning C, Huang J, et al. Pre-exposure prophylaxis for the prevention of HIV infection in high risk populations: A meta-analysis of randomized controlled trials. PLoS ONE. 2014;9(2). [reason: meta-analysis of existing RCTs]

25. K RA, McMahan V, Goicochea P, Vargas L, Marcus JL, Grant RM, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. AIDS and behavior. 2012;16(5):1243-59. [reason: secondary analysis of iPrEX]

26. Koester KA, Liu A, Eden C, Amico KR, McMahan V, Goicochea P, et al. Acceptability of drug detection monitoring among participants in an open-label pre-exposure prophylaxis study. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2015;27(10):1199-204. [reason: observational study on subset of iPrEX OLE study]

27. Koss CA, Bacchetti P, Hillier SL, Livant E, Horng H, Mgodi N, et al. Differences in Cumulative Exposure and Adherence to Tenofovir in the VOICE, iPrEx OLE, and PrEP Demo Studies as Determined via Hair Concentrations. AIDS Research and Human Retroviruses. 2017;33(8):778-83. [reason: secondary analysis of 3 studies]

28. Lehman DA, Baeten JM, McCoy CO, Weis JF, Peterson D, Mbara G, et al. Risk of drug resistance among persons acquiring HIV within a randomized clinical trial of single-or

dual-agent preexposure prophylaxis. Journal of Infectious Diseases. 2015;211(8):1211-8. [reason: secondary analysis of Partners PrEP study]

29. Liu A, Glidden DV, Anderson PL, Amico KR, McMahan V, Mehrotra M, et al. Patterns and correlates of PrEP drug detection among MSM and transgender women in the global iPrEx study. Journal of Acquired Immune Deficiency Syndromes. 2014;67(5):528-37. [reason: secondary analysis of iPrEX]

30. Liu AY, Vittinghoff E, Chillag K, Mayer K, Thompson M, Grohskopf L, et al. Sexual risk behavior among HIV-uninfected men who have sex with men participating in a tenofovir preexposure prophylaxis randomized trial in the United States. Journal of acquired immune deficiency syndromes (1999). 2013;64(1):87-94. [reason: secondary analysis of US CDC Safety Study]

31. Lorente N, Fugon L, Carrieri MP, Andreo C, Le Gall JM, Cook E, et al. Acceptability of an on-demand pre-exposure HIV prophylaxis trial among men who have sex with men living in France. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2012;24(4):468-77. [reason: acceptability study prior to RCT]

32. Markowitz M, Frank I, Grant RM, Mayer KH, Elion R, Goldstein D, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. The lancet HIV. 2017;4(8):e331-e40. [reason: intervention different (cabotegravir)]

33. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Chuachoowong R, Mock PA, et al. Enrollment characteristics and risk behaviors of injection drug users participating in the Bangkok Tenofovir Study, Thailand. PLoS One. 2011;6(9):e25127. [reason: secondary analysis of Bangkok tenofovir study enrolment characteristics]

34. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Risk behaviors and risk factors for HIV infection among participants in the Bangkok tenofovir study, an HIV pre-exposure prophylaxis trial among people who inject drugs. PLoS One. 2014;9(3):e92809. [reason: secondary analysis of Bangkok tenofovir study enrolment characteristics]

35. McCormack SM, Noseda V, Molina JM. PrEP in Europe - Expectations, opportunities and barriers. Journal of the International AIDS Society. 2016;19. [reason: not a RCT; review article]

36. Mehrotra ML, Westreich D, McMahan VM, Glymour MM, Geng E, Grant RM, et al. Baseline Characteristics Explain Differences in Effectiveness of Randomization to Daily Oral TDF/FTC PrEP Between Transgender Women and Cisgender Men Who Have Sex With Men in the iPrEx Trial. Journal of acquired immune deficiency syndromes (1999).

2019;81(3):e94-e8. Epub 2019/06/14. doi: 10.1097/qai.0000000000002037. [reason: secondary analysis iPrEX]

37. Mills A, Workowski K, Campbell T, Benson P, Crofoot G, Salazar L, et al. Renal outcomes for participants taking F/TAF vs. F/TDF for HIV PrEP in the DISCOVER trial. Open Forum Infectious Diseases. 2019;6:S64. doi: 10.1093/ofid/ofz359.139. [reason: review; no efficacy data]

38. Miltz AR, Lampe FC, Bacchus LJ, McCormack S, Dunn D, White E, et al. Intimate partner violence, depression, and sexual behaviour among gay, bisexual and other men who have sex with men in the PROUD trial. BMC public health. 2019;19(1):431. Epub 2019/04/27. doi: 10.1186/s12889-019-6757-6.. [reason: secondary analysis PROUD]

39. Mugwanya KK, Donnell D, Celum C, Thomas KK, Ndase P, Mugo N, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis. The lancet Infectious diseases [Internet]. 2013; 13(12):[1021-8 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/297/CN-00915297/frame.html. [reason: longitudinal analysis of Partners PrEP]

40. Mujugira A, Baeten JM, Donnell D, Ndase P, Mugo NR, Barnes L, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. Plos one [Internet]. 2011; 6(10):[e25828 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/232/CN-00805232/frame.html. [reason: secondary analysis Partners PrEP]

41. Murnane PM, Brown ER, Donnell D, Coley RY, Mugo N, Mujugira A, et al. Estimating Efficacy in a Randomized Trial With Product Nonadherence: Application of Multiple Methods to a Trial of Preexposure Prophylaxis for HIV Prevention. American Journal of Epidemiology. 2015;182(10):848-56. [reason: secondary analysis Partners PrEP]

42. Murnane PM, Celum C, Mugo N, Campbell JD, Donnell D, Bukusi E, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS (london, england) [Internet]. 2013; 27(13):[2155-60 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/174/CN-01000174/frame.html. [reason: secondary analysis Partners PrEP]

43. Ndase P, Celum C, Campbell J, Bukusi E, Kiarie J, Katabira E, et al. Successful discontinuation of the placebo arm and provision of an effective HIV prevention product after a positive interim efficacy result: the partners PrEP study experience. Journal of acquired immune deficiency syndromes (1999) [Internet]. 2014; 66(2):[206-12 pp.]. Available from: http://cochranelibrary-

wiley.com/o/cochrane/clcentral/articles/717/CN-00992717/frame.html. [reason: review of Partners PrEP]

44. O'Halloran C, Rice B, White E, Desai M, D TD, McCormack S, et al. Chemsex is not a barrier to self-reported daily PrEP adherence among PROUD study participants. International Journal of Drug Policy. 2019;74:246-54. doi: 10.1016/j.drugpo.2019.10.007 [reason: secondary analysis PROUD]

45. Page K, Tsui J, Maher L, Choopanya K, Vanichseni S, Philip Mock M, et al. Biomedical HIV prevention including pre-exposure prophylaxis and opiate agonist therapy for women who inject drugs: State of research and future directions. Journal of Acquired Immune Deficiency Syndromes. 2015;69:S169-S75. [reason: review; not a RCT]

46. Post F, Spinner C, Coll P, Hawkins T, Anderson J, Zhong L, et al. DISCOVER in Europe: A sub-analysis of the phase 3 randomized, controlled trial of daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP). HIV Medicine. 2019;20:243-4. doi: 10.1111/hiv.12815. [reason: abstract only/no full text available]

47. Roux P, Fressard L, Suzan-Monti M, Chas J, Sagaon-Teyssier L, Capitant C, et al. Is on-Demand HIV Pre-exposure Prophylaxis a Suitable Tool for Men Who Have Sex With Men Who Practice Chemsex? Results From a Substudy of the ANRS-IPERGAY Trial. Journal of acquired immune deficiency syndromes (1999). 2018;79(2):e69-e75. Epub 2018/09/14. doi: 10.1097/qai.0000000000001781. [reason: secondary analysis IPERGAY]

48. Ruane PJ, Clarke A, Post FA, Schembri G, Jessen H, Trottier B, et al. Phase 3 randomized, controlled DISCOVER study of daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP): Week 96 results. HIV Medicine. 2019;20:95-6. doi: 10.1111/hiv.12815. [reason: abstract only/no full text available]

49. Sacks HS. Preexposure tenofovir-emtricitabine reduced HIV infection in men who have unprotected anal sex with men. Annals of Internal Medicine. 2016;164(2):JC3. [reason: review of PROUD]

50. Spinner CD, Brunetta J, Shalit P, Prins M, Cespedes M, Brainard D, et al. DISCOVER study for HIV pre-exposure prophylaxis (PrEP): F/TAF has a more rapid onset and longer sustained duration of HIV protection compared with F/TDF. Journal of the International AIDS Society. 2019;22. doi: 10.1002/jia2.25327. [reason: abstract only/no full text available]

51. Thomson KA, Baeten JM, Mugo NR, Bekker LG, Celum CL, Heffron R. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. Current Opinion in HIV and AIDS. 2016;11(1):18-26. [reason: review; not a RCT]

52. Velloza J, Bacchetti P, Hendrix CW, Murnane P, Hughes JP, Li M, et al. Short- and Long-Term Pharmacologic Measures of HIV Pre-exposure Prophylaxis Use Among High-Risk Men Who Have Sex With Men in HPTN 067/ADAPT. Journal of acquired immune deficiency syndromes (1999). 2019;82(2):149-58. Epub 2019/07/25. doi: 10.1097/qai.0000000000002128. [reason: secondary analysis HPTN 067/ADAPT]

53. Vermund SH. Safety and tolerability of tenofovir for preexposure prophylaxis among men who have sex with men. Journal of Acquired Immune Deficiency Syndromes. 2013;64(1):3-6. [reason: review; not a RCT]

54. White E, Dunn DT, Desai M, Gafos M, Kirwan P, Sullivan AK, et al. Predictive factors for HIV infection among men who have sex with men and who are seeking PrEP: a secondary analysis of the PROUD trial. Sexually transmitted infections. 2019;95(6):449-54. Epub 2019/03/29. doi: 10.1136/sextrans-2018-053808.. [reason: secondary analysis PROUD]

55. Wohl D, Ruane P, Hosek S, Creticos C, Morris S, Phoenix J, et al. Bone safety outcomes with F/TAF vs. F/TDF for PrEP in the DISCOVER trial. Open Forum Infectious Diseases. 2019;6:S464. doi: 10.1093/ofid/ofz360.1151. [reason: review; no efficacy data]

56. Yacoub R, Nadkarni GN, Weikum D, Konstantinidis I, Boueilh A, Grant RM, et al. Elevations in serum creatinine with tenofovir-based HIV pre-exposure prophylaxis: A meta-analysis of randomized placebo-controlled trials. Journal of Acquired Immune Deficiency Syndromes. 2016;71(4):e115-e8. [reason: meta-analysis of RCTs]

S3.2

Risk of Bias assessment

Two studies were open-label trials and, as such, blinding of participants or investigators was not possible. A further three studies were placebo-controlled trials that additionally investigated alternate dosing schedules; while participants and investigators were blinded to drug assignment, they could not be blinded to regimen assignment. One study contained a 'no pill' arm that could not be blinded in addition to a placebo arm. Two studies had unclear risk for reporting bias due to the fact that study protocols were not available. Figure S1 represents the review authors' judgements about each risk of bias item for each included study.

Figure S1. Risk of bias summary

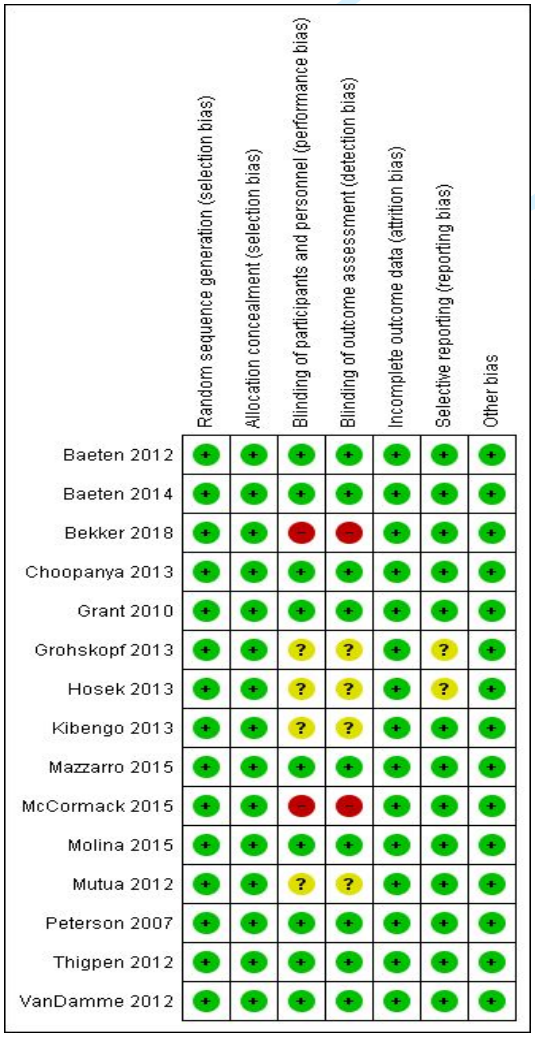
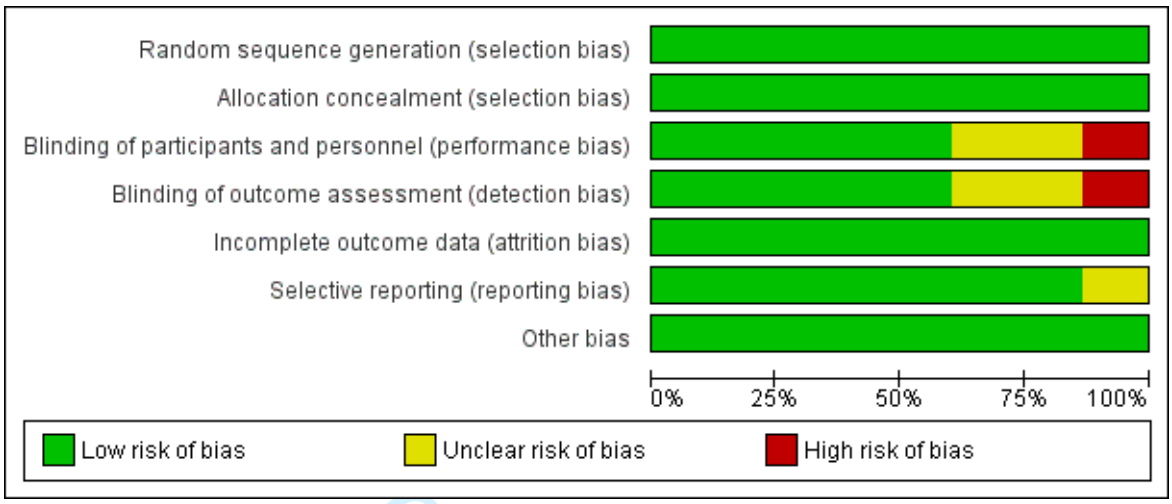


Figure S2 represents the review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure S2. Risk of bias graph



S3.3

Adherence, as measured in primary studies

Study	Intervention	Adherence
Bekker 2018 (ADAPT Cape Town)	Tenofovir/emtricitabine (daily, time and event-driven PrEP)	• 75% (7,283 of 9,652 doses taken) for daily regimen; 65% (2,367 of 3,616 doses taken) for time-driven regimen and 53% (1,161 of 2,203 doses taken) for those event-driven regimen by electronic drug monitoring.
Baeten 2012 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (three arms: two active arms and one placebo arm)	• Factoring in missed visits, other reasons for non-dispensation of study medication and non-adherence to dispensed study pills, 92.1% of follow-up time was covered by study medication. • Among 29 subjects on the tenofovir and emtricitabine/tenofovir arms who acquired HIV-1, 31% had tenofovir detected in a plasma sample at the seroconversion visit compared with 82% of 902 samples from a randomly-selected subset of 198 subjects who did not acquire HIV-1.
Baeten 2014 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (two active arms)	• Study medication was taken by participants on 90.0% of days during follow-up time (factoring in protocol-defined study medication interruptions, missed visits, and non-adherence to dispensed study pills, as measured by monthly pill counts of returned study tablets). • Among subjects who acquired HIV-1, the minority (14/51, 27.5%) had tenofovir detected in a plasma sample at the visit at which HIV-1 seroconversion was detected, compared with the majority (1,047/1,334, 78.5%) of samples from a randomly selected subset of subjects who did not acquire HIV-1.
Choopanya 2013 (Bangkok Tenofovir Study)	Tenofovir (daily)	• Adherence was assessed daily at directly observed therapy (DOT) visits and monthly at non-DOT visits using a study drug diary. On the basis of participants' study drug diaries, participants took the study drug an average (mean) of 83.8% of days. • Plasma samples were obtained from 46 participants with incident HIV infections the day infection was detected, and from 282 HIV-negative participants to test for the presence of tenofovir. Tenofovir was detected in one (1%) of 177 participants in the placebo group and 100 (66%) of 151 participants in the tenofovir group. • In the case-control analysis in participants assigned to tenofovir, tenofovir was detected in the plasma of 5 (39%) of 13 HIV-positive participants and 93 (67%) of 138 HIV-negative participants.
Grant 2010 (iPrEx)	Tenofovir/emtricitabine (daily)	• The rate of self-reported pill use was lower in the emtricitabine–tenofovir group than in the placebo group at week 4 (mean, 89% vs. 92%) and at week 8 (mean, 93% vs. 94%) but was similar thereafter (mean, 95% in the two groups). • The percentage of pill bottles returned was 66% by 30 days and 86% by 60 days. • Among subjects in the emtricitabine–tenofovir group, at least one of the study-drug components was detected in 3 of 34 subjects with HIV infection (9%) and in 22 of 43

		seronegative control subjects (51%).
Grohskopf 2013 (CDC Safety Study)	Tenofovir (daily)	• Adherence was measured by pill count, medication event monitoring system (MEMS) and self-report; adherence ranged from 77% (pill count) to 92% (MEMS).
Kibengo 2013 (IAVI Uganda Study)	Tenofovir/emtricitabine (daily or intermittent)	• Median MEMS adherence rates were 98% (IQR: 93–100) for daily PrEP regimen, 91% (IQR: 73–97) for fixed intermittent dosing and 45% (IQR: 20–63) for post-coital dosing. • There was no difference in adherence rates between active and placebo groups, thus these two groups were combined for the adherence analyses.
Hosek 2013 (Project PrEPare)	Tenofovir/emtricitabine (daily)	• Self-reported medication adherence averaged 62% (range 43–83%) while rates of detectable tenofovir in plasma of participants in the emtricitabine/tenofovir arm ranged from 63.2% (week 4) to 20% (week 24).
Mazzarro 2015 (VOICE)	Tenofovir (oral), tenofovir/emtricitabine (oral) and vaginal tenofovir gel (all daily)	• 90% by self-report, 86% by returned products and 88% as assessed with audio computer-assisted self-interviewing (ACASI). • In a random sample, tenofovir was detected in 30%, 29% and 25% of available plasma samples from participants randomly assigned to receive tenofovir, tenofovir/emtricitabine and tenofovir gel, respectively.
McCormack 2015 (PROUD)	Tenofovir/emtricitabine (daily)	• Overall, sufficient study drug was prescribed for 88% of the total follow-up time. • Tenofovir was detected in plasma of all 52 sampled participants (range 38–549 ng/mL) who reported that they were taking PrEP.
Molina 2015 (Ipergay)*	Tenofovir/emtricitabine (intermittent)	• Median pills per month: 15 pills. • In the tenofovir–emtricitabine group, the rates of detection were 86% for tenofovir and 82% for emtricitabine, respectively, a finding that was consistent with receipt of each drug within the previous week. Tenofovir and emtricitabine were also detected in eight participants in the placebo group, three of whom were receiving postexposure prophylaxis. • Computer-assisted structured interviews also performed to assess most recent sexual episode. Overall, 28% of participants did not take tenofovir-emtricitabine or placebo, 29% took the assigned drug at a suboptimal dose and 43% took the assigned drug correctly.
Mutua 2012 (IAVI Kenya Study)	Tenofovir/emtricitabine (daily or intermittent)	• There was no difference in adherence rates between treatment and placebo groups, thus these groups were combined for the adherence analyses. Median MEMS adherence rates were 83% (IQR: 63–92) for daily dosing and 55% (IQR:28–78) for fixed intermittent dosing (p=0.003).
Peterson 2007 (West Africa Study)	Tenofovir (daily)	• The amount of product used was estimated by subtracting the number of pills returned from the number dispensed, and dividing this number by the total number of days in the effectiveness analysis. • Drug was used no more than 69% of study days. Excluding time off product due to pregnancy, drug was used for no more than 74% of study days.

Thigpen 2012 (TENOFOVIR2)	Tenofovir/emtricitabine (daily)	• The two groups had similar rates of adherence to the study medication as estimated by means of pill counts (84.1% in the tenofovir–emtricitabine group and 83.7% in the placebo group, P = 0.79) and self-reported adherence for the preceding 3 days (94.4% and 94.1%, respectively; P = 0.32). • Among the four participants in the tenofovir–emtricitabine group who became infected with HIV during the study, two (50%) had detectable levels of tenofovir and emtricitabine in plasma obtained at the visit before and closest to their estimated seroconversion dates. among the 69 participants, matched by sample date, who did not undergo seroconversion, 55 (80%) and 56 (81%) had detectable levels of tenofovir and emtricitabine, respectively.
VanDamme 2012 (FEM-PrEP)	Tenofovir/emtricitabine (daily)	• At the time of study-drug discontinuation, 95% of participants reported that they had usually or always taken the assigned drug. Pill-count data were consistent with ingestion of the study drug on 88% of the days on which it was available to the participants. • In contrast, drug-level testing revealed much lower levels of adherence. Among women with seroconversion in the tenofovir–emtricitabine group, the target plasma level of tenofovir was identified in 7 of 27 women (26%) at the beginning of the infection window (excluding six women for whom the window started at enrolment), in 7 of 33 (21%) at the end of the window, and in 4 of 27 (15%) at both visits. Among the uninfected control participants, the numbers of women with target-level tenofovir were somewhat higher: 27 of 78 women (35%) at the beginning of the infection window, 35 of 95 (37%) at the end of the window, and 19 of 78 (24%) at both visits.

Tenofovir = Tenofovir Disoproxil Fumarate

* non-daily regimen

S3.4

Results from Thigpen 2012 (by gender)

	Tenofovir-emtricitabine group	Placebo group	Efficacy	95% CI	95% CI
Female	7	14	49.4	-21.5, 80.8	0.11
Male	2	10	80.1	24.6, 96.9	0.03

Cohort is modified intention-to-treat

S3.5

Change in sexual behaviour/STI rates

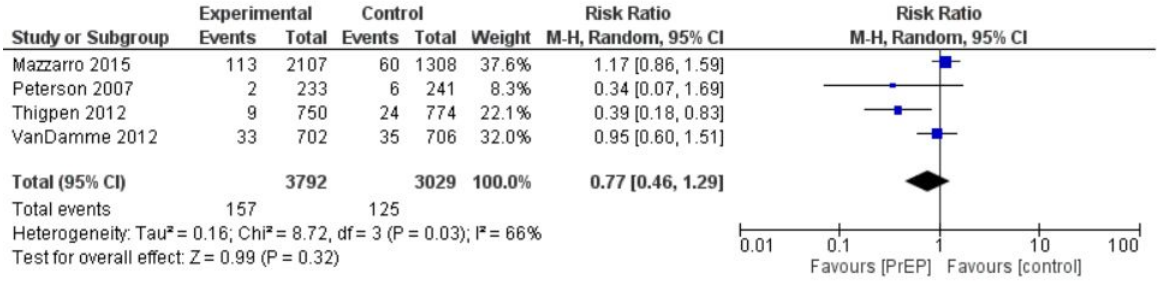
Study	Measure	Outcome
Baeten 2012 (Partners PrEP)	• Having sex without a condom with HIV-positive partners in prior month • STI diagnoses from sex acts outside partnership	• At enrolment, 27% of HIV-1 seronegative partners reported sex without condoms with their HIV-1 seropositive partner during the prior month. This percentage decreased during follow-up (to 13% and 9% at 12 and 24 months) and was similar across the study arms. • The proportion reporting outside partnerships and who acquired sexually transmitted infections during follow up did not differ across the study arms.
Baeten 2014 (Partners PrEP)	Unreported	
Bekker 2018 (ADAPT Cape Town)	Unreported	
Choopanya 2013 (Bangkok Tenofovir Study)	• Drug use behaviour • Number of sexual partners	• Tenofovir and placebo recipients reported similar rates of injecting and sharing needles and similar numbers of sexual partners during follow up with no interactions between time and treatment group. • Overall, number of participants reporting injecting drugs or sharing needles reduced over time. • Sex with more than one partner decreased from 522 (22%) at enrolment to 43 (6%) at month 72.
Grant 2010 (iPrEx)	• Number of anal sex acts • Proportion of anal sex acts with a condom • STI diagnoses	• Sexual practices were similar in the two groups at all time points. • The total numbers of sexual partners with whom the respondent had receptive anal intercourse decreased, and the percentage of those partners who used a condom increased after subjects enrolled in the study. • There were no significant between-group differences in the numbers of subjects with syphilis, gonorrhea, chlamydia, genital warts or genital ulcers during follow-up.
Grohskopf 2013 (CDC Safety Study)	Unreported	
Hosek 2013 (Project PrEPare)	Male-to-male unprotected anal sex acts	• No significant differences among the three treatment groups across visits. • Insignificant trend from baseline to week 24 of decreasing unprotected anal sex acts across all treatment arms.
Kibengo 2013 (IAVI Uganda Study)	HIV behaviour change	• The median number of sexual partners in the past month remained at 1 (IQR: 1–1) during the trial. • No other HIV risk behaviours reported at baseline changed during the trial
Mazzarro 2015 (VOICE)	Unreported	
McCormack 2015 (PROUD)	• Number of sexual partners • Incident STIs	• Total number of different anal sex partners varied widely between baseline and year 1. No significant difference between groups at one year was detected. • Proportion with confirmed rectal chlamydia/gonorrhea was similar in immediate and delayed arms (proxy for condomless anal intercourse). • Adjusted odds ratio for rectal chlamydia or gonorrhea: 1.00

		(0.72–1.38) (adjusted for number of sexual health screens)
Molina 2015 (Ipergay)	• Total number of sexual intercourse events • Proportion of events without a condom • Number of sexual partners • Incident STIs	• Sexual practices did not change overall among the participants during the study period as compared with baseline: there were no significant between group differences in the total number of episodes of sexual intercourse in the four weeks before, in the proportion of episodes of receptive anal intercourse without condoms, or in the proportion of episodes of anal sex without condoms during the most recent sexual intercourse. • There was a slight but significant decrease in the number of sexual partners within the past two months in the placebo group as compared with the tenofovir—emtricitabine group (7.5 and 8, respectively; p = 0.001). • The proportions of participants with a new sexually transmitted infection (of the throat, anus, and urinary tract combined) during follow-up were similar, with 41% in the tenofovir—emtricitabine group and 33% in the placebo group (P = 0.10).
Mutua 2012 (IAVI Kenya Study)	HIV behaviour change	• The median number of sexual partners in the past month increased from three (IQR 2–4) at baseline to four (IQR 2–8) at month 4 during the trial. • Because there may have been underreporting of sex partners at baseline, authors also compared the median number of sexual partners month 2 (4) and at month 4 (4).
Peterson 2007 (West Africa Study)	• Condom use at last sex • Number of sex acts • Number of partners	• During screening, participants reported an average of 12 coital acts per week with an average of 21 sexual partners in the previous 30 days (including 11 new partners). During follow-up, participants reported an average of 15 coital acts per week, with an average of 14 sexual partners in the previous 30 days (six new partners). Of note, most participants in this study were sex workers. • Self-reported condom use increased from 52% at screening (average across all sites during the last coital act prior to screening) to approximately 92% at the enrolment, month 3, month 6, and month 9 visits, to 95% at the month 12 visit (for acts occurring during the last seven days). The average condom use during the follow-up period was 92%.
Thigpen 2012 (TENOFOVIR2)	• Protected sex episodes with main/ most recent casual partner • Number of sexual partners	• The percentage of sexual episodes in which condoms were used with the main or most recent casual sexual partner was similar in the two study groups at enrolment (81.4% [range, 76.6 to 86.4] in the tenofovir–emtricitabine group and 79.2% [range, 71.6 to 87.6] in the placebo group, P = 0.66) and remained stable over time. • The reported number of sexual partners declined in both groups during the course of the study.
VanDamme 2012 (FEM-PrEP)	• Number of partners • Sex acts without a condom • Pelvic STIs	• There was no evidence of increased HIV risk behaviour during the trial, with modest but significant reductions in the numbers of partners (mean reduction, 0.14; P<0.001 by paired-data t-test), vaginal sex acts (mean reduction, 0.58; P<0.001), and sex acts without a condom (mean reduction, 0.46; P<0.001) reported by women at the last follow-up visit, as compared with seven days before enrolment. • Fewer than half the study participants agreed to undergo a pelvic examination. There were no significant between-group differences in the prevalence of pelvic STIs.

Supplementary Material 4: Additional figures and forest plots

Efficacy

Figure S3. Meta-analysis: HIV acquisition in heterosexual participants, PrEP versus placebo

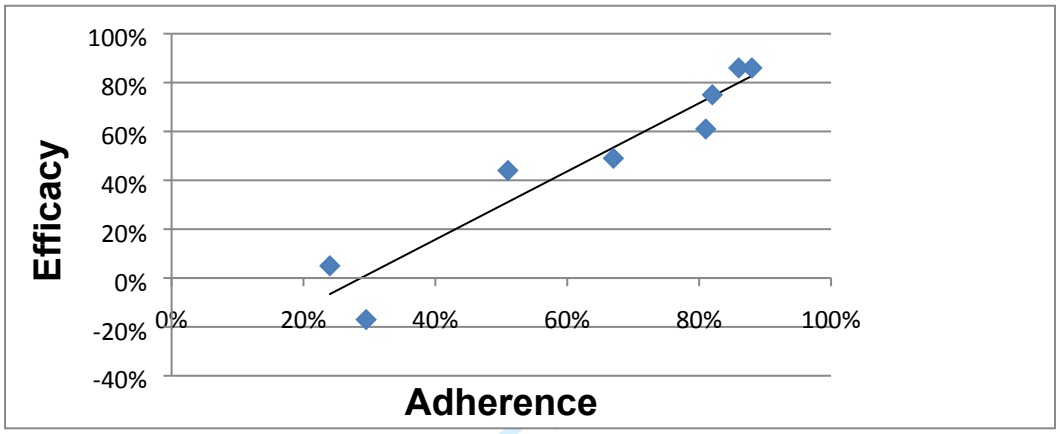


Supplementary Material

Adherence

Figure S3 compares efficacy and adherence (measured by plasma drug concentration; n=7 trials). A regression model yielded a R^2 of 0.92 ($p<0.001$).

Figure S4. Efficacy as a function of adherence



Caption: Only trials that reported plasma drug concentrations contributed to anlaysis: (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), Thigpen 2012 (TDF2 study), VanDamme 2012 (FEM-PrEP)

Safety

Figure S5. Meta-analysis: 'any adverse event', PrEP versus placebo

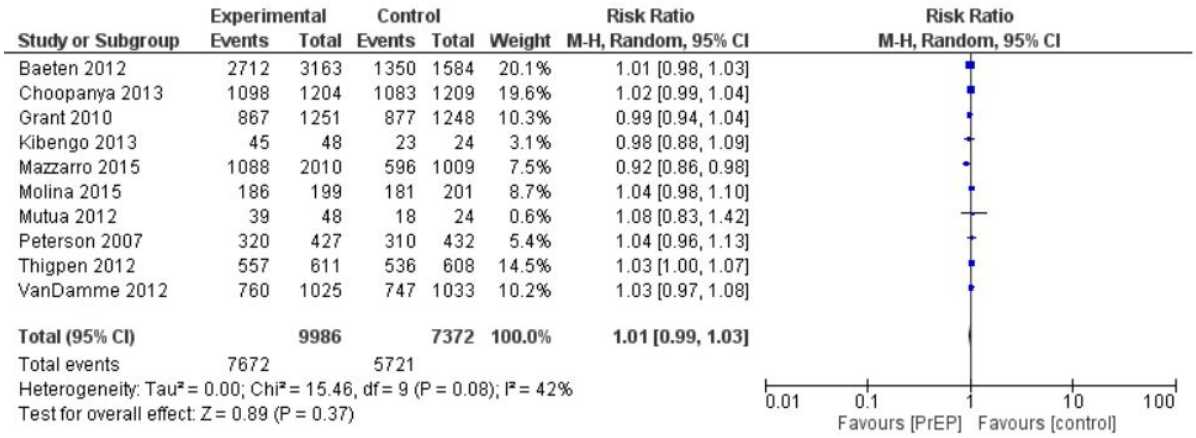


Figure S6. Meta-analysis: 'any adverse event', tenofovir/emtricitabine versus tenofovir

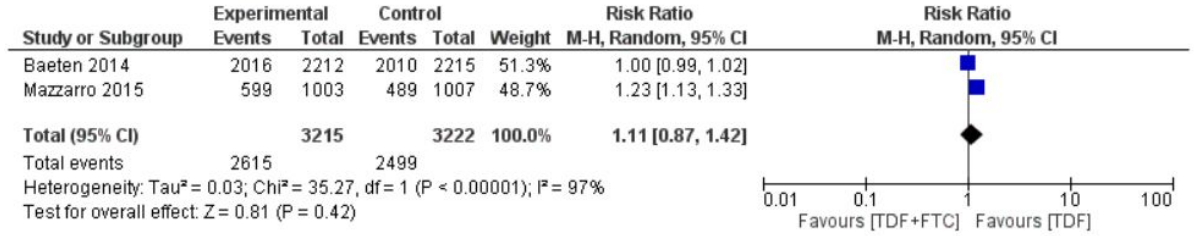
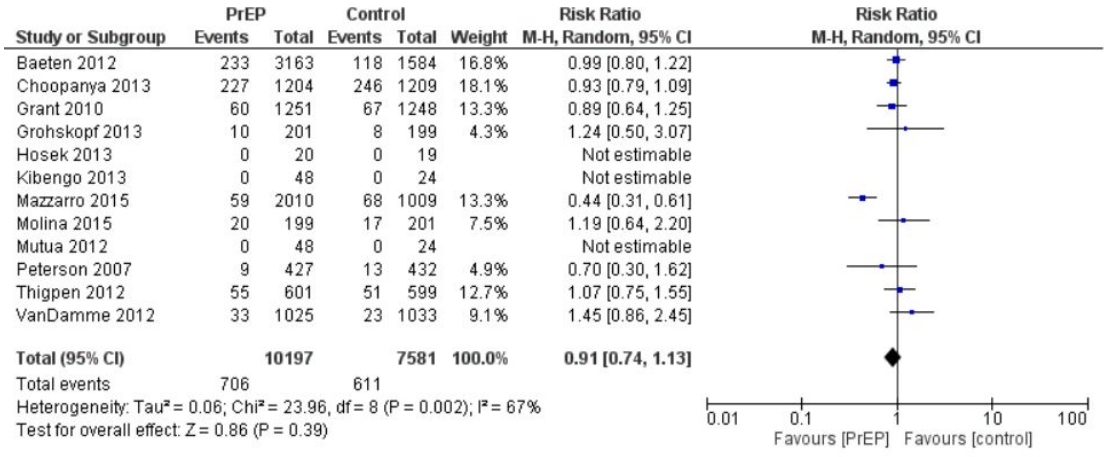
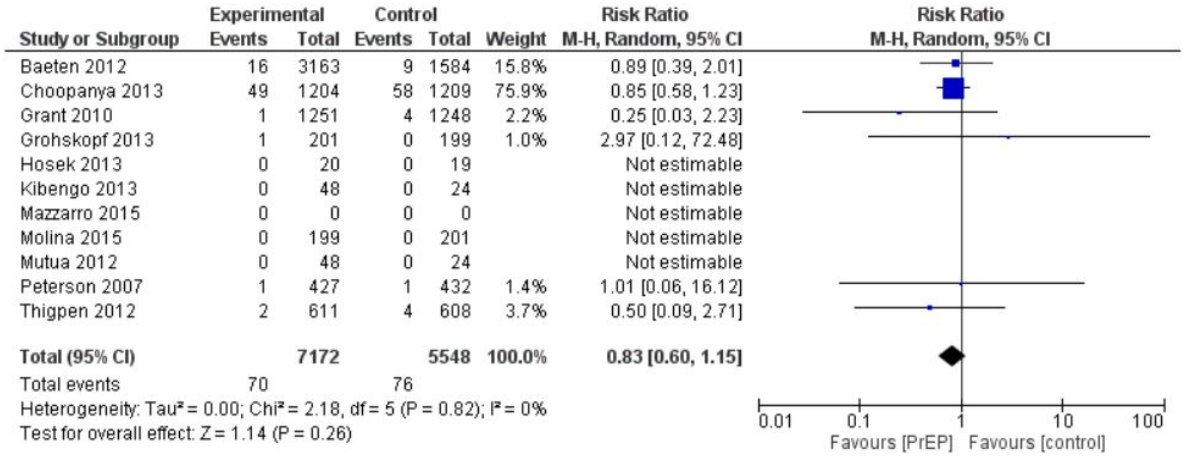


Figure S7. Meta-analysis: serious adverse events, PrEP versus placebo



Supplementary Material

Figure S8. Meta-analysis: deaths, PrEP versus placebo



Viral drug resistance mutations

Figure S9. Meta-analysis: any drug mutation (acute HIV at enrolment), PrEP versus placebo

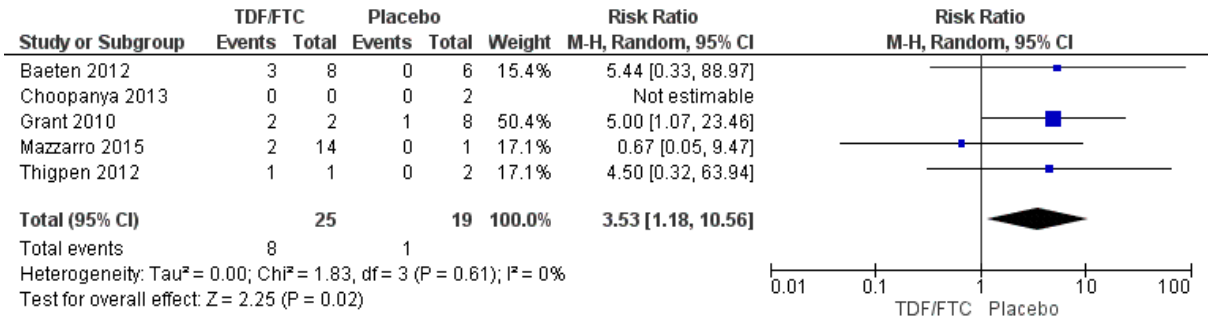
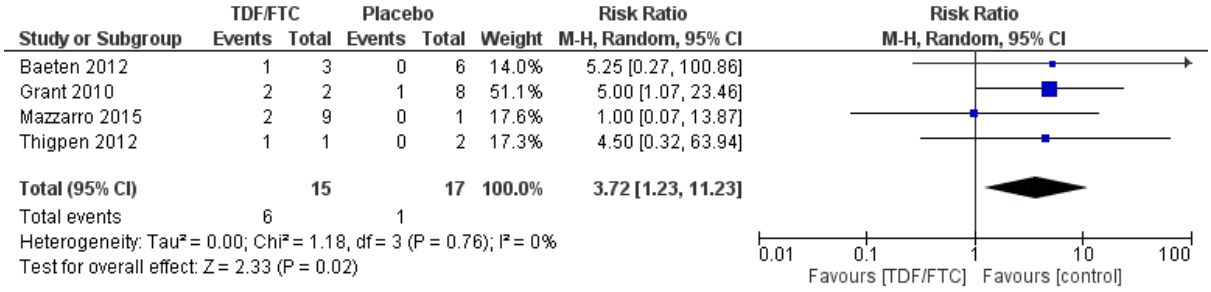


Figure S10. Meta-analysis: emtricitabine mutation (acute HIV at enrolment), tenofovir/emtricitabine versus placebo



Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

	Reporting Item	Page Number
Title		
#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract		

Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	6
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	7
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	8

Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	8
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material 2
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	7
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	8
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	Supplementary Material 2
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	8

Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	9
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	13
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Supplementary Material 2

Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	16-23 and Supplementary Material 2
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	16-23 and Supplementary Material 2
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	GRADE assessment and Supplementary Material 2
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	21
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	25
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	26

Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28

Funding

Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	1

Notes:

- 8: Supplementary Material 2
- 11: Supplementary Material 2
- 19: Supplementary Material 2
- 20: 16-23 and Supplementary Material 2
- 21: 16-23 and Supplementary Material 2
- 22: GRADE assessment and Supplementary Material 2 This checklist was completed on 20. December 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Oral Pre-exposure Prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048478.R1
Article Type:	Original research
Date Submitted by the Author:	04-Oct-2021
Complete List of Authors:	O Murchu, Eamon; Health Information and Quality Authority; Trinity College Marshall, Liam; Health Information and Quality Authority Teljeur, Conor; Health Information and Quality Authority Harrington, Patricia; Health Information and Quality Authority Hayes, Catherine; University of Dublin Trinity College, Public Health and Primary Care Moran, Patrick; Health Information and Quality Authority; Trinity College Ryan, Mairin; Health Information and Quality Authority; Trinity College, Department of Pharmacology & Therapeutics
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Infectious diseases, Health policy, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, PUBLIC HEALTH, INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Oral Pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations

Authors: Eamon O Murchu, MB BCh BAO, MPH;[a, b] Liam Marshall, MSc;[a] Conor Teljeur, PhD;[a] Patricia Harrington, PhD;[a] Catherine Hayes, MD, MPH, MB;[b] Patrick Moran, PhD;[a, b] Máirín Ryan, PhD.[a, c]

[a]Health Information and Quality Authority, George's Court, George's Lane, Dublin 7, Ireland

[b]Trinity College Dublin, Institute of Population Health, Tallaght, Dublin 24, Ireland

[c]Trinity College Dublin, Department of Pharmacology & Therapeutics, Trinity Health Sciences, Dublin 8, Ireland

Corresponding author: Eamon O Murchu. Trinity College Dublin, Institute of Population Health, Tallaght, Dublin 24, Ireland. E-mail: eamonvalmont@gmail.com.

Word count: Abstract=300; Main text (excluding abstract, tables, figures, references): 4,698.

Figures=3; **Tables**=4; **Supplementary Material**=2 (S1 – protocol, S2 – search strategy, S3 – additional results); **PRISMA Checklist**=1

Abstract

Objective

The objective of this study was to conduct a systematic review and meta-analysis of randomised controlled trials (RCTs) of the effectiveness and safety of oral Pre-Exposure Prophylaxis (PrEP) to prevent HIV.

Methods

Databases (PubMed, Embase and the Cochrane Register of Controlled Trials) were searched up to 5/7/2020. RCTs were included that compared oral tenofovir-containing PrEP to placebo, no treatment or alternative medication/dosing schedule. The primary outcome was the rate ratio (RR) of HIV infection using a modified intention-to-treat analysis. All analyses were stratified a priori by population: men who have sex with men (MSM), serodiscordant couples, heterosexuals and people who inject drugs (PWID).

The quality of individual studies was assessed using the Cochrane Risk-of-Bias tool and the certainty of evidence was assessed using GRADE.

Results

Of 2,803 unique records, 15 RCTs met our inclusion criteria. Over 25,000 participants were included, encompassing 38,289 person-years of follow-up data.

PrEP was found to be effective in MSM (Rate Ratio [RR] 0.25, 95% CI: 0.1-0.61; Absolute Rate Difference [ARD] -0.03, 95% CI: -0.01 to -0.05), serodiscordant couples (RR 0.25, 95% CI: 0.14-0.46; ARD -0.01, 95% CI: -0.01 to -0.02) and PWID (RR 0.51, 95% CI: 0.29-0.92; ARD -0.00, 95% CI: -0.00 to -0.01), but not in heterosexuals (RR 0.77, 95% CI: 0.46-1.29).

Efficacy was strongly associated with adherence (p<0.01). PrEP was found to be safe, however unrecognised HIV at enrolment increased the risk of viral drug resistance mutations. Evidence for behaviour change or an increase in STIs was not found.

Conclusions

PrEP is safe and effective in MSM, serodiscordant couples and PWID. Additional research is needed prior to recommending PrEP in heterosexuals. Data were limited by poor adherence in several studies. No RCTs reported effectiveness or safety data for other high-risk groups, such as transgender women and sex workers.

PROSPERO ID: CRD42017065937

Keywords: 'PrEP', 'pre-exposure prophylaxis', 'HIV'

Article Summary

Strengths and limitations of this study

- A systematic review and meta-analysis of RCTs was conducted of the efficacy and safety of oral PrEP to prevent HIV following best practice guidelines (PRISMA guidelines and GRADE framework)
- Observational studies were excluded from this review, and as such, PrEP effectiveness may be lower in real-world settings
- Change in sexual behaviour, or 'risk compensation', is difficult to ascertain based on RCT evidence alone
- Due to substantial variation in adherence across studies, findings should be interpreted with caution.

Introduction

While the incidence of HIV has declined worldwide over the past decade, 1.5 million new HIV infections occurred in 2020,[1] highlighting the ongoing need for new and effective HIV prevention initiatives. Pre-exposure prophylaxis (PrEP) is a novel biomedical form of HIV prevention method, whereby oral anti-retrovirals (most commonly a combination of tenofovir and emtricitabine) are taken by individuals at high risk of HIV acquisition to prevent infection. PrEP aims to complement the existing arsenal of HIV prevention strategies, such as the promotion of safer sex practices, treatment-as-prevention and post-exposure prophylaxis after sexual exposure.

In 2014, the WHO recommended offering PrEP to men who have sex with men (MSM),[2] based a 2010 trial that demonstrated the effectiveness in this group.[3] Subsequently, in 2015, they broadened the recommendation to include anyone at substantial risk of HIV infection (defined as risk of 3 per 100 person-years in the absence of PrEP),[4] based on further evidence of the acceptability and effectiveness in other populations. While the success of early PrEP studies in MSM was replicated in the years that followed (with high efficacy noted in IPERGAY[5] and PROUD[6] clinical trials), uncertainty still exists in other key populations. Many initial studies that failed to demonstrate effectiveness were plagued by poor adherence, such as those that enrolled heterosexual women.[7] Also, of major concern to public health officials and policy-makers is the potential occurrence of 'risk compensation' in PrEP users (an increase in unsafe sexual practices due to the knowledge that PrEP is protective against HIV), which may lead to an increase in STIs, exacerbating the secular trend of rising STI rates in many countries.

Since the most recent WHO recommendation, a number of new trials in diverse populations have been conducted. We therefore conducted a systematic review and meta-analysis to retrieve the most up-to-date evidence on the effectiveness and safety of oral PrEP compared with placebo, no treatment or alternative oral PrEP medication/dosing schedule in all populations, with a particular emphasis on adherence and risk compensation. This review aimed to inform the decision of the Irish government to implement a PrEP programme and to assist in the development of national clinical practice guidelines on PrEP for HIV prevention.

Methods

A systematic review and meta-analysis of randomised controlled trials (RCTs) was conducted, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[9] This framework is commonly used internationally to aid decisions by policy-makers, and ensured a systematic and transparent approach in the development of clinical practice recommendations. This study was registered with PROSPERO (ID: CRD42017065937) and followed an agreed protocol (Supplementary Material 1).

Search strategy and selection criteria

Electronic searches were conducted in Medline (PubMed), Embase, the Cochrane Register of Controlled Trials, CRD DARE Database, Morbidity and Mortality Weekly Report (CDC), and Eurosurveillance reports. Search terms that related to 'HIV' were combined with search terms that related to 'PrEP' or 'tenofovir', and filters for study design (RCTs) were applied (the full search strategy for PubMed is provided in Supplementary Material 2). Databases were searched on 5 July 2020. No restrictions were placed based on location of the intervention or date of publication. No language restrictions were used; articles in languages other than English were translated where necessary. Table 1 outlines the inclusion criteria for study selection. Animal studies, studies that did not report primary outcome data (HIV incidence), and abstracts from conference proceedings were excluded.

It was decided a priori that all analyses of effectiveness would be stratified by population. The four populations were men who have sex with men (MSM), serodiscordant

heterosexual couples (individuals whose partners are HIV positive and not virally suppressed on antiretroviral medications), heterosexuals and people who inject drugs (PWIDs).

Table 1. Inclusion criteria for studies

Population	Populations at substantial risk of HIV, including men who have sex with men, serodiscordant heterosexual couples, heterosexuals and people who inject drugs
Intervention	Oral tenofovir-containing pre-exposure prophylaxis
Comparator	Placebo, no treatment or alternative oral PrEP medication/dosing schedule
Outcomes	Primary outcome: Relative risk of HIV infection Secondary outcomes: 1. Adherence to PrEP 2. Adverse events 3. Incidence of other STIs and behaviour change associated with PrEP use 4. Viral drug mutations among those who contract HIV
Studies	RCTs

Legend: PrEP – pre-exposure prophylaxis, RCT – randomised controlled trial, STI – sexually transmitted infection.

Data collection and analysis

Results of the database search were exported to Endnote X7. Full text articles were obtained for all citations identified as potentially eligible. Two reviewers (EOM and LM) independently screened these according to the pre-specified inclusion criteria. Two reviewers (EOM and LM) independently performed data extraction and assessed the risk of bias according to the Cochrane Risk of Bias tool.[10] An overall assessment of the quality of the evidence was assessed using the GRADE approach that included an assessment of other biases, such as publication bias.[9]

The primary outcome measure was the rate ratio (RR) of HIV infection for each population. The rate of HIV infection represented the number of HIV infections that occurred per person-years of follow up data, and the RR compares the rate of HIV infection in the PrEP group with control. The rate of HIV infection (per person-years) was favoured over risk of HIV infection as rate incorporates both the number of participants *and* the duration of

follow-up, allowing for comparisons across studies that may vary significantly in terms of study duration. The absolute rate difference (ARD) of HIV infection was also estimated for each population; in this case, the ARD represented the actual difference in the observed rate of HIV between PrEP and control groups per person-year of follow-up data. Meta-analyses of RRs and ARDs were performed in Review Manager 5.3 using Mantel-Haenszel random effects models.

A modified intention-to-treat analysis was employed (and not per-protocol analysis); therefore, effectiveness was a function of both efficacy of the drug itself and on adherence. A modified intention-to-treat analysis was selected instead of a standard intention-to-treat analysis to account for unrecognised HIV infection at enrolment. In the modified intention-to-treat analysis, all patients who were HIV negative at enrolment in the study were included in analyses, and individuals with an unrecognised HIV infection prior to enrolment were excluded.

Clinical heterogeneity was assessed by the reviewers based on the description of the interventions and comparators in the RCTs. Statistical heterogeneity was examined using the I^2 statistic (I^2 values above 75% represented considerable heterogeneity). If there was sufficient clinical homogeneity across studies, results were pooled using a random effects Mantel–Haenszel model.

In the estimation of PrEP effectiveness, subgroups of studies were defined by dosing schedule, comparator and adherence. Analyses were stratified by population and adherence. Adherence was dichotomised for subgroup analyses: if the proportion of participants who were adherent was ≥80%, the study was considered ‘high adherence’ and <80% was considered ‘low adherence’. Commonly used measures of adherence include self-

report, pill counts, medication event monitoring systems (MEMS), structured interviews and plasma drug detection methods. Plasma drug monitoring is considered the gold standard for adherence assessment; plasma drug detection was favoured over self-report/pill count in the determination of adherence as it minimises recall bias. In studies that only measured plasma drug concentration in participants who reported taking study drug, the proportion of samples with study drug detected was multiplied by the self-reported adherence rate. In studies that measured adherence in a number of ways without undertaking plasma drug monitoring, taking a conservative approach, the lowest estimate of adherence was used for subgroup analysis.

To investigate the relationship between efficacy and adherence, a meta-regression analysis was conducted (meta-regression was considered the appropriate model as it accounts for trial size in analyses). In this analysis, adherence was a continuous variable, and only studies that confirmed adherence through plasma drug monitoring were included. Analyses were conducted in R version 3.6.2.

In the assessment of the safety of PrEP, the definitions for adverse events and serious adverse events followed the definitions used in the primary studies. Outcome measures were expressed as both RRs of safety events and RDs between groups. In the assessment of behaviour change, the effect of PrEP on condom use, number of sexual partners, recreational drug use and the rate of new STI diagnoses (as a proxy for condomless sex) were assessed. In the assessment of PrEP-related drug mutations, subgroups included patients with unrecognised acute HIV infection at the time of enrolment and patients who seroconverted during the course of the trial. Where there was a lack of data or agreed definitions for these outcomes, a narrative review was performed.

In the case of pooling data for rare events, there can be issues with the inclusion of studies with zero events in one or both arms.[11] A common approach where there are zero events in one arm is to apply a continuity correction, whereby all cells in the two by two table for a given study have 0.5 added to avoid division by zero. This approach can lead to bias, particularly for small trials or those with imbalanced arms. Trials with zero events in both arms are typically excluded, leading to a loss of information. Approaches are available to include zero event trials with application of a continuity correction. For this study, if trials with zero events in one or both arms were identified, a sensitivity analysis using a random effects Poisson regression[11] and beta-binomial[12] models was applied to determine whether the results were sensitive to presence of trials with zero events in one or both arms. The main analysis excluded trials with zero events in both arms, as has been recommended when a treatment effect is considered likely.[13]

In the assessment of publication bias, funnel plots were used when there were more than 10 studies available for analysis. Standard approaches to funnel plots and tests for small study bias use the log(OR) or log(RR), which are not independent of their estimated standard error creating a bias. Those tests also have the limitation that they omit studies that have zero events in both arms. To overcome these issues, the arcsine test for publication bias was used.[14]

Patient and public involvement

Patients or the public were not involved in this research.

Ethics approval statement

This study did not require ethics approval as no human participants were involved.

Results

A total of 2,803 unique records were retrieved, resulting in 73 studies for full text review (Figure 1 provides the PRISMA diagram of study selection and the list of excluded studies, along with reasons, is provided in Supplementary Material 3.1). Fifteen RCTs met our inclusion criteria and were included in the assessment of effectiveness and safety. Seven RCTs were placebo-controlled trials that evaluated daily oral PrEP.[3 7 15-19] Two studies randomised participants to receive either immediate or delayed PrEP.[6 20] Three placebo-controlled trials investigated non-daily PrEP, including intermittent and 'on-demand' (also known as event-based) PrEP.[5 21 22] Two RCTs did not contain a 'no PrEP' arm (placebo or no medication): one compared tenofovir with tenofovir/emtricitabine[23] and one compared three different PrEP dosing schedules.[24] One study contained three arms: PrEP, placebo and 'no pill'.[25] Four distinct patient populations were assessed. Six RCTs enrolled MSM,[3 5 6 20 21 25] five enrolled heterosexual participants,[7 16 17 19 24] three enrolled serodiscordant couples[18 22 23] and one enrolled PWIDs.[15]

Figure 1. PRISMA diagram of study selection

Figure 1 Legend: Diagram provides details on the selection process of studies for inclusion. Note that the exclusion of 2,703 citations at the 'screening' stage did not meet our study inclusion/exclusion criteria based on screening of title/abstract.

Included studies involved 25,051 participants encompassing 38,289 person-years of follow-up data. Of the 15,062 participants that received active drug in the intervention arms of trials, 55% received combination tenofovir/emtricitabine and 45% received single agent tenofovir. Follow-up periods ranged from 17 weeks to 6.9 years. Four trials were conducted in high-income countries (USA, England, France and Canada), 10 in low- or middle-income

countries (including nine trials in sub-Saharan Africa) and one was a multicenter trial conducted across four continents. All studies reported the results of a modified intention-to-treat analysis.

The main characteristics of included studies are provided in Table 2.

Table 2. Study characteristics

Study	Location	Population	Intervention	Comparison	No. participants	Follow-up (PYs)	Adherence: high (≥80%) vs. low (<80%)*
MSM							
Hosek 2013 (Project PrEPare)[25]	USA	MSM. Median age: 20 years	TDF/FTC	Daily PrEP vs placebo or 'no pill'	58	27	Low: 62% by self-report
Grohskopf 2013 (CDC Safety Study)[20]	USA	MSM. Age range: 18–60 years	TDF	Immediate or delayed PrEP vs immediate or delayed placebo	400	800	Low: 77% by pill count
iPrEx (Grant 2010)[3]	Brazil, Ecuador, South Africa, Peru, Thailand, USA	MSM (99%) and transgender women (1%). Age range: 18–67 years.	TDF/FTC	Daily PrEP vs placebo	2499	3324	Low: 51% by plasma drug detection
McCormack 2015 (PROUD)[6]	UK	MSM. Median age: 35 years	TDF/FTC	Immediate PrEP vs delayed PrEP	544	504	High: 88% (self-report and plasma drug detection**)
Molina 2015 (IPERGAY)[5]	Canada, France	MSM. Median age 34.5 years	TDF/FTC	Intermittent ('on demand') PrEP vs placebo***	400	431	High: 86% by plasma drug detection
Mutua 2012 (IAVI Kenya Study)[21]	Kenya	MSM (93%) and female sex workers (7%). Mean age: 26 years	TDF/FTC	Daily or intermittent PrEP vs daily or intermittent placebo	72	24	High: 83% by MEMS
Serodiscordant heterosexual couples (when the HIV-positive partner is not on antiretroviral treatment)							
Kibengo 2013 (IAVI Uganda Study)[22]	Uganda	Serodiscordant couples (negative partner: 50% male). Mean age: 33 years	TDF/FTC	Daily or intermittent PrEP vs daily or intermittent placebo	72 couples	24	High: 98% by MEMS
Baeten 2012 (Partners PrEP Study)[18]	Kenya, Uganda	Serodiscordant couples (negative partner: 61–64% male). Age range: 18–45 years	TDF/FTC and TDF only	Daily PrEP vs placebo	4,747 couples	7,830	High: 82% by plasma drug detection

Study	Location	Population	Intervention	Comparison	No. participants	Follow-up (PYs)	Adherence: high (≥80%) vs. low (<80%)*
Baeten 2014 (Partners PrEP Study Continuation)[23]	Kenya and Uganda	Serodiscordant couples (negative partner: 62–64% male). Age range: 28–40 years	TDF/FTC and TDF only	TDF/FTC vs TDF	4,410 couples	8,791	Low: 78.5% by plasma drug detection
Heterosexuals							
Bekker 2018 (ADAPT Cape Town)[24]	South Africa	Women. Median age: 26 years	TDF/FTC	Daily, time and event-driven PrEP	191	99	Low: 53-75% by MEMS
Marrazzo 2015 (VOICE)[19]	South Africa, Uganda, Zimbabwe	Women. Median age: 24 years	5 arms: TDF/FTC, TDF only, 1% TDF vaginal gel, oral placebo and placebo vaginal gel	Daily PrEP vs placebo	4,969	5,509	Low: 29% by plasma drug detection
Peterson 2007 (West African Safety Study)	Nigeria, Cameroon, Ghana	Women. Age range: 18–34 years	TDF	Daily PrEP vs placebo	936	428	Low: 69% by pill count
Thigpen 2012 (TENOFOVIR2)[16]	Botswana	Heterosexual men (54.2%) and women (45.8%). Age range: 18–39 years	TDF/FTC	Daily PrEP vs placebo	1219	1,563	High: 84.1% by pill count
VanDamme 2012 (FEM-PrEP)[7]	Tanzania, South Africa, Kenya	Women. Median age: 24.2 years	TDF/FTC	Daily PrEP vs placebo	2,120	1407	Low: 24% by plasma drug detection
PWIDs							
Choopanya 2013 (Bangkok Tenofovir Study)[15]	Thailand	PWID (80% male). Median age: 31 years	TDF	Daily PrEP vs placebo	2,413	9,665	Low: 67% by plasma drug detection

Table 2 Legend: FTC = emtricitabine. MSM = men who have sex with men; PWID = people who inject drugs. TDF = Tenofovir Disoproxil Fumarate. TDF/FTC = Tenofovir Disoproxil Fumarate and Emtricitabine fixed dose combination. MEMS = Medication Event Monitoring System. PY = person-years. UK = United Kingdom. USA = United States of America. In all cases, tenofovir dose was 300mg and emtricitabine dose was 200mg.

*Adherence refers to the proportion of participants in trials that adhered to study drug. In most studies, more than one method was used to measure adherence; taking a conservative approach, the lowest estimate of adherence was used. In trials that investigated daily and intermittent PrEP, adherence relates to daily PrEP. In studies that measured tenofovir and emtricitabine separately, adherence refers to tenofovir detection.

**PROUD trial: adherence was determined by a combination of self-report and plasma drug detection. Sufficient study drug was prescribed for 88% of the total follow-up time, and study drug was detected in 100% of participants who reported taking PrEP.

***'On demand' dosing: participants were instructed to take 2 pills of TDF/FTC or placebo 2 to 24 hours before sex, followed by a third pill 24 hours later and a fourth pill 48 hours later.

All included individual RCTs were judged to have a low risk of bias by the Cochrane Risk of Bias Tool (risk of bias graph and summary provided in Supplementary Material 3.2). Across studies, while publication bias may have been present in earlier, industry-funded studies (with fewer participants), this form of bias was considered less likely in the more recent, larger, publicly-funded studies. To investigate publication bias, the arcsine test for funnel plot asymmetry was applied to all 13 trials (as there were too few trials in individual population groups). The p-values for the equivalent of the Begg, Egger and Thompson tests were 0.58, 0.14 and 0.13, respectively. As such, it was determined that there was no evidence of funnel plot asymmetry (Supplementary Material 3.3).

Effectiveness

The following sections present the effectiveness of PrEP to prevent HIV acquisition by study population and stratified by adherence, where appropriate. Tables 3 and 4 present the GRADE 'summary of findings' assessment of the effectiveness and safety of PrEP.

Table 3. GRADE summary of findings: PrEP effectiveness

Summary of findings table: Effectiveness of PrEP

Patient or population: HIV prevention in participants at substantial risk
Intervention: PrEP
Comparison: no PrEP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect, expressed as rate ratios (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Rate with no PrEP	Rate with PrEP				
HIV infection: **MSM** (all clinical trials)	40 per 1,000	**10 per 1,000** (4 to 24)	**RR 0.25** (0.10 to 0.61)	5,103 (6 RCTs)	⊕⊕⊕⊕ HIGH [a, b]	PrEP is effective in preventing HIV acquisition in MSM with a rate reduction of 75%
HIV infection: **MSM**, trials with high (≥80%) adherence	66 per 1,000	**9 per 1,000** (4 to 23)	**RR 0.14** (0.06 to 0.35)	960 (3 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is highly effective in preventing HIV acquisition in MSM in trials with high adherence (over 80%) with a rate reduction of 86%
HIV infection: **MSM**, trials with low (<80%) adherence**	32 per 1,000	**18 per 1,000** (12 to 26)	**RR 0.55** (0.37 to 0.81)	4143 (3 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing HIV acquisition in MSM in trials with low adherence (under 80%) with a rate reduction of 45%
HIV infection: **Serodiscordant couples***** (all clinical trials: two studies with high [≥80%] adherence)	20 per 1,000	**5 per 1,000** (3 to 9)	**RR 0.25** (0.14 to 0.46)	5,237 (2 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing HIV acquisition in serodiscordant couples with a rate reduction of 75%
HIV infection: **Heterosexual transmission** (all clinical trials)	41 per 1,000	**32 per 1,000** (19 to 53)	**RR 0.77** (0.46 to 1.29)	6,821 (4 RCTs)	⊕⊕◯◯ LOW[a, c]	PrEP is not effective in preventing heterosexual HIV transmission (all trials)
HIV infection: **Heterosexual transmission**, trials with high (≥80%) adherence	31 per 1,000	**12 per 1,000** (6 to 26)	**RR 0.39** (0.18 to 0.83)	1524 (1 RCT)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing heterosexual HIV transmission in heterosexuals in one trial with high (over 80%) adherence. This trial enrolled males and females; note that efficacy was only reported for males.

HIV infection: **Heterosexual transmission**, trials with low (<80%) adherence	45 per 1,000	**46 per 1,000** (34 to 64)	**RR 1.03** (0.75 to 1.43)	5297 (3 RCTs)	⊕⊕⊕◯ MODERATE[c]	PrEP is not effective in preventing heterosexual HIV transmission in trials with low adherence. Note that all three trials enrolled heterosexual women.
HIV infection: **People who inject drugs** (all clinical trials: one study with low [<80%] adherence)	7 per 1,000	**3 per 1,000** (2 to 6)	**RR 0.51** (0.29 to 0.92)	9,666 (1 RCT)	⊕⊕⊕◯ MODERATE[d]	PrEP is effective in preventing HIV transmission in people who inject drugs with a rate reduction of 49%

Table 3 Legend:
Explanations
a. Downgraded one level for heterogeneity b. Upgraded one level for large effect (RR<0.5) c. Downgraded one level for imprecision d. Downgraded one level for indirectness
***The rate in the intervention group** (and its 95% confidence interval) is based on the assumed rate in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Note that under alternative methods to account for zero events in one or both arms (beta-binomial), there is greater imprecision and the upper confidence bound crosses the line of no effect
***In studies that enrolled serodiscordant couples, the HIV-positive individual was not on antiretroviral therapy. All studies relate to serodiscordant heterosexual couples.
CI: Confidence interval; **RR:** Rate ratio
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 4. GRADE summary of findings: Safety of PrEP

Summary of findings table: Safety of PrEP

Patient or population: HIV prevention in participants at substantial risk. **Intervention**: PrEP. **Comparison**: no PrEP.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Rate with no PrEP	Rate with PrEP				
Safety outcome: Any adverse event	776 per 1,000	**784 per 1,000** (768 to 799)	**RR 1.01** (0.99 to 1.03)	17,358 (10 RCTs)	⊕⊕⊕⊕ HIGH	Adverse events do not occur more commonly in patients taking PrEP compared with placebo. Adverse events were common in trials (78% of patients reporting 'any' event).
Safety outcome: Serious adverse events	81 per 1,000	**73 per 1,000** (60 to 91)	**RR 0.91** (0.74 to 1.13)	17,778 (12 RCTs)	⊕⊕⊕⊕ HIGH	Serious adverse events do not occur more commonly in patients taking PrEP compared with placebo. Serious adverse events occurred in 7% of patients in trials but most were not drug related.
Safety outcome: Deaths	13 per 1,000	**10 per 1,000** (8 to 15)	**RR 0.83** (0.60 to 1.15)	12,720 (11 RCTs)	⊕⊕⊕◯ MODERATE[a]	Deaths did not occur more commonly in people taking PrEP compared with placebo in trials. No deaths were related to PrEP.
Safety outcome: Drug resistance mutations in patients with acute HIV at enrolment	53 per 1,000	**186 per 1,000** (62 to 556)	**RR 3.53** (1.18 to 10.56)	44 (5 RCTs)	⊕⊕⊕◯ MODERATE[a]	Patients randomised to receive PrEP who had acute HIV at enrolment were at increased risk of developing resistance mutations to the study drug. Most conferred resistance to emtricitabine.

Table 4 Legend:
Explanations
a. Imprecision was detected due to few observations.
Note that only a minority of studies tested for viral drug resistance mutations
*The rate in the intervention group (and its 95% confidence interval) is based on the assumed rate in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Rate ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Effectiveness in MSM

Six studies enrolled MSM.[3 5 6 20 21 25] A meta-analysis of all studies resulted in a RR of 0.25 (95% CI: 0.1 to 0.61), indicating a 75% reduction in the rate of HIV acquisition (Figure 2). The estimated absolute rate reduction (ARD) was -0.03 (95% CI: -0.01 to -0.05), indicating PrEP users had a 3% lower rate of HIV acquisition per person-year of follow-up.

When stratified by adherence, heterogeneity was eliminated (I^2 reduced from 52% to 0%). PrEP was most effective in studies with high adherence, as expected, where rate of HIV acquisition was reduced by 86% (RR 0.14, 95% CI: 0.06 to 0.35; ARD -0.06, 95% CI: -0.04 to -0.09; I^2 = 0%, n=3 studies).[5 6 21] Of the three studies with high adherence, one study was small and reported non-significant findings due to few events (Mutua et al.[21]). Of the remaining two studies, one study investigated daily PrEP use (McCormack et al., PROUD trial[6]) and the other investigated 'on demand' PrEP (Molina et al., IPERGAY trial[5]). Both studies reported identical efficacy (PROUD: RR 0.14, 95% CI 0.04-0.47; IPERGAY: RR 0.14, 95% CI 0.03-0.6).

When adherence was under 80%, acquisition rate was reduced by 45% (RR 0.55, 95% CI: 0.37 to 0.81; ARD -0.01, 95% CI: -0.00 to -0.02; I^2 = 0%, n=3 studies).[3 20 23 25]

Figure 2. Meta-analysis: HIV acquisition in MSM, all studies

Figure 2 Legend: Forest plot of the meta-analysis of HIV incidence in all MSM trials, PrEP versus placebo or no drug. Subgroups include high (≥80%) adherence and low (<80%) adherence. 'Events' refers to new HIV infections and 'Total' refers to total person-years at risk during the study period.

Effectiveness in serodiscordant heterosexual couples

In all three studies that enrolled serodiscordant heterosexual couples, the HIV-infected partner was not on antiretroviral therapy (studies were conducted in Kenya and Uganda; HIV-infected participants did not meet criteria for ART initiation at the time of enrolment).[18 22 23] Details on the CD4 count (a type of cell that HIV infects) or viral load of the HIV-infected partners were not reported.

Two studies investigated the effect of daily oral PrEP compared to placebo.[18 22] A total of 4,819 couples were enrolled, and the seronegative individual was male in the majority (>60%) of cases. One trial enrolled few participants (n=24 in the daily PrEP arm), and the duration of the trial was very short (4 months); this study did not contribute to analyses as no seroconversions were reported in either arm of the trial.[22] The trial by Baeten et al.[18] consisted of three arms: tenofovir/emtricitabine (n=1,568 participants), tenofovir alone (n=1,572 participants) and placebo (n=1,568 participants). Tenofovir/emtricitabine resulted in a 75% rate reduction (RR 0.25, 95% CI: 0.14 to 0.46; ARD -0.01, 95% CI: -0.01 to -0.02) and tenofovir alone resulted in a 67% rate reduction (RR 0.33, 95% CI: 0.19 to 0.56; ARD -0.01, 95% CI: -0.01 to -0.02). A continuation of this trial (Baeten et al. 2014[23]) compared tenofovir/emtricitabine with tenofovir alone: there was no significant difference between groups.

Effectiveness in heterosexuals

Of the five studies enrolling heterosexual participants, four were placebo-controlled[7 16 17 19] and one compared different drug schedules.[24] Four studies enrolled only women[7 17 19 24] and one study enrolled both men and women.[16] All studies were conducted in a high HIV prevalence context (countries in Sub-Saharan Africa). A meta-analysis of all placebo-controlled studies did not demonstrate a statistically significant reduction in HIV acquisition

(RR 0.77, 95% CI: 0.46 to 1.29; I^2 = 66%, Figure S4, Supplementary Material 3.4). In the only trial with high adherence (Thigpen et al.[16]), a rate reduction of 61% was noted (RR 0.39, 95% CI 0.18 to 0.83; ARD -0.02, 95% CI: -0.01 to -0.04). This was the only trial to enrol both men and women, and when the results were analysed separately by sex, efficacy was only noted in males, with a rate reduction of 80% (RR 0.2, 95% CI 0.04 to 0.91, Supplementary Material 3.5). As expected, in a meta-analysis of trials with low adherence, the result was non-significant (RR 1.03, 95% CI 0.75 to 1.43, I^2 = 21%, Figure S5, Supplementary Material 3.4).

A final study compared different PrEP regimens (daily PrEP, 'time-driven' PrEP and 'event-driven' PrEP).[24] Fewer infections occurred in the daily PrEP arm; however, there were no significant differences in HIV acquisition comparing either event or time-driven PrEP with daily PrEP.

Effectiveness in PWID

Only one study enrolled PWID.[15] Daily oral tenofovir was found to be effective, with a 49% reduction in HIV acquisition (RR 0.51, 95% CI: 0.29 to 0.92; ARD -0.00, 95% CI: -0.00 to -0.01). In this study, HIV transmission may have occurred sexually or parenterally.

Sensitivity analysis

A sensitivity analysis was applied to determine whether the use of continuity correction and the omission of studies with zero events in both arms impacted on the results. First, a meta-analysis of all trials was conducted. Both the Poisson regression and beta-binomial models produced similar results to the standard approach (Table 5), providing reassurance that the impact of excluding smaller studies with zero events was small. Second, a meta-analysis of studies in the MSM group was undertaken, stratified by adherence, as these analyses

included three studies with zero events in one or both arms (Table 5). Only the beta-binomial model converged on a stable result. The rate ratio and 95% confidence interval were very similar to the main analysis for the high adherence group. However, there was greater imprecision in the low adherence group, and the wider confidence bounds included the possibility of no effect.

Table 5 Sensitivity analysis

Group	Method of analysis	Rate ratio	95% CI
All studies (n=13)	Standard approach (Mantel-Haenszel)	0.41	0.26 to 0.67
	Poisson regression	0.375	0.225 to 0.625
	Beta-binomial	0.437	0.210 to 0.911
MSM group: high adherence (n=3 studies)	Standard approach (Mantel-Haenszel)	0.14	0.06 to 0.35
	Beta-binomial	0.134	0.063 to 0.284
MSM group: low adherence (n=3 studies)	Standard approach (Mantel-Haenszel)	0.55	0.37 to 0.81
	Beta-binomial	0.428	0.038 to 4.815

Relationship between efficacy and adherence

A meta-regression analysis was performed to investigate the relationship between efficacy and adherence, accounting for trial size (Figure 3). Adherence was measured in a variety of methods across trials (Supplementary Material 3.6). Studies that did not confirm adherence through plasma drug detection rates were excluded from meta-regression analyses, due to biases associated with other methods such as self-report or pill count.

Efficacy (as RRs) and adherence (by proportion with plasma drug detectable) were strongly associated ($p<0.001$). As the proportion adherent increases from 0.5 to 0.6, the RR decreases by 0.13. Therefore, on average, a 10% decrease in adherence decreases efficacy by 13%.

Figure 3. Fitted meta-regression line of the relationship between trial-level PrEP adherence and efficacy

Figure 3 Legend: Only trials that reported plasma drug concentration from a representative sample contributed to analysis, represented as circles (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), VanDamme 2012 (FEM-PrEP). The solid line represents the fitted regression line and the shaded area the 95% Confidence Interval. The X-axis represents the trial-level adherence as a proportion and the Y-axis represents the efficacy as rate ratios.

Safety

Eleven studies reported data on 'any' adverse events, including ten that compared PrEP with placebo[3 5 7 15-19 21 22] and two that compared tenofovir alone to tenofovir/emtricitabine.[19 23] A meta-analysis of placebo-controlled trials demonstrated no significant difference between groups (RR 1.01; 95% CI 0.99 to 1.03; I^2 = 42%, Figure S7, Supplementary Material 3.4). Comparing tenofovir with tenofovir/emtricitabine, one study noted a small increase in adverse events in the tenofovir/emtricitabine group (RR 1.23; 95% CI 1.03 to 1.33, Figure S8, Supplementary Material 3.4)[19] and another failed to show any difference.[23]

Of note, several studies reported mild decreases in renal function among PrEP users that returned to normal following discontinuation of PrEP use, while a reduction in creatinine clearance (a measure of renal function) was not observed in others.[15 18] Where renal function has been affected, PrEP was associated with mild, non-progressive and reversible reductions in creatinine clearance.[3 5 6 15 18] Some trials also found slight decreases in bone mineral density.[16 19]

All 15 studies reported data in relation to the risk of serious adverse events: 12 were placebo-controlled,[3 5 7 15-22 25] one compared PrEP with no PrEP[6], two compared tenofovir/emtricitabine with tenofovir[19 23] and one compared different dosage schedules.[24] A meta-analysis of placebo-controlled trials did not find an increased risk (RR 0.91, 95% CI: 0.74 to 1.13; I^2 = 67%, Figure S9, Supplementary Material 3.4).

In the only trial that compared PrEP with no treatment, an increased rate of serious adverse events was noted in the treatment arm (RR 3.42; 95% CI 1.4 to 8.35).[6] However, these adverse events were not considered study drug-related. Two studies compared tenofovir with tenofovir/emtricitabine: one found no significant difference between groups[23] and another found an increased rate in the tenofovir/emtricitabine group (RR 2.48; 95% CI: 1.42 to 4.33).[19] Of note, not all studies defined what constituted adverse events (including serious adverse events).

No study found an increased mortality rate associated with PrEP use, and of the deaths that occurred, none were considered to be drug-related (Figure S10, Supplementary Material 3.4).

Viral drug resistance mutations

Five placebo-controlled trials provided data on HIV mutations among patients who had acute HIV infection at enrolment (unknown to study investigators).[3 15 16 18 19] In total, there were 44 seroconversions at enrolment, 25 who received study drug and 19 who received placebo. There were nine mutations detected, eight among participants receiving study drug and one in a patient receiving placebo. The RR for any drug mutation was 3.53 (95% CI: 1.18 to 10.56; I^2 = 0%, Figure S11, Supplementary Material 3.4) which represents an ARD of

0.57 (95% CI: 0.21 to 0.94).

Of the nine resistance mutations at enrolment, seven were for emtricitabine. The RR for emtricitabine mutation was 3.72 (95% CI: 1.23 to 11.23; I^2 = 0%) which represents an ARD of 0.6 (95% CI: 0.23 to 0.97) in those receiving tenofovir/emtricitabine (Figure S12, Supplementary Material 3.4).[3 16 18 19]

Among participants who seroconverted postrandomisation, the development of resistant mutations was uncommon. Of 551 seroconverters, only seven resistance mutations were detected; one tenofovir mutation was noted in a tenofovir-only arm (k65n, a rare tenofovir resistance mutation) and six emtricitabine mutations were noted.

Risk compensation

Changes in sexual behaviour, or 'risk compensation', was measured in a number of ways, including condom use, number of sexual partners, changes in STI rates and recreational drug use. Due to the differences in how sexual behaviour was reported across trials, including differing definitions and at different time points, a meta-analysis was not possible.

Studies consistently showed no between-group difference in condom use or number of sexual partners. Studies showed either no overall change in condom use throughout the duration of the study (n=4 studies) or an increase in condom use (n=4 studies). Most studies showed no change in the number of sexual partners over time (n=6 studies), four studies showed a slight reduction in number of sexual partners and one showed an increase (investigators of this study noted the possibility of partner underreporting at baseline[21]). No study reported an increase in STIs or a between-group difference in STI diagnoses. In the only study to enroll intravenous drug users, a reduction in intravenous drug use, needle

sharing and number of sexual partners over the course of the study was noted.[15] Supplementary Material 3.7 presents full details of behaviour change and STI rates in individual studies.

Discussion

Summary of findings

This systematic review and meta-analysis of 25,051 individuals encompassing 38,289 person-years of follow-up data confirms that oral tenofovir-containing PrEP is both effective and safe. PrEP is particularly effective in MSM, with a rate reduction of 75% across all trials, rising to 86% in trials with high adherence. Only one trial investigated the effectiveness of 'on demand' PrEP.[5] This trial reported a rate reduction of 86%, identical to the only comparable trial among daily PrEP users[6] (both trials enrolled a large sample of MSM and achieved high levels of adherence). PrEP is also effective in serodiscordant couples, and no significant difference exists between single-agent tenofovir and combination tenofovir/emtricitabine.

Questions remain regarding PrEP effectiveness in other populations. One study found that PrEP was effective in PWID.[15] However, a limitation of this study is that investigators were not sure if transmission was parenteral or sexual. It is unclear if PrEP is effective in heterosexuals. PrEP was effective in preventing heterosexual HIV transmission in one trial where adherence was high (61% reduction),[16] but only in male participants. The remaining three heterosexual trials, all conducted in sub-Saharan Africa, only enrolled females and adherence was noted to be very low.[7 17 19]

Adherence varied greatly across studies, ranging from 25% to 88% by plasma drug monitoring. As expected, efficacy was found to be strongly associated with adherence ($p<0.01$). On average, a 10% reduction in adherence reduced efficacy by 13%.

PrEP was found to be safe, and there was no difference in adverse event rates comparing single agent tenofovir with tenofovir/emtricitabine in combination. Some studies noted a

transient elevation of creatinine with resolution upon discontinuation of study drug.[3 5 6 15 18] While uncommon, viral drug resistance mutations may occur in the presence of an unrecognised HIV infection at enrolment.

Our findings of high effectiveness in MSM has been confirmed by two open-label extensions[26 27] that followed the conclusion of four RCTs included in this review.[3 5 20 25] One open-label extension found no seroconversions in participants that took a minimum of four pills per week.[26]

Ongoing studies

Following the conclusion of this review, an additional search was conducted to identify recently published or ongoing RCTs after the date of our database search. PubMed was searched, using the same search strategy, up to 9 September 2021. No additional PrEP efficacy trials were identified, although two publications were identified that relate to an ongoing non-inferiority RCT that compared two different types of oral tenofovir-containing PrEP: tenofovir alafenamide plus emtricitabine versus tenofovir disoproxil fumarate plus emtricitabine[28 29] (all studies in this systematic review relate to tenofovir disoproxil fumarate). Interim results found that the daily tenofovir alafenamide group showed non-inferior efficacy to the daily tenofovir disoproxil fumarate group for HIV prevention, and the number of adverse events for both regimens was low. Tenofovir alafenamide had more favourable effects on bone mineral density and biomarkers of renal safety than tenofovir disoproxil fumarate,[28] however there was more weight gain among participants who had received tenofovir alafenamide (median weight gain 1.7 kg vs 0.5 kg, p<0.0001).[29]

Strengths and limitations

This systematic review assessed the use of PrEP in all potentially eligible populations, and provided a GRADE assessment of important outcomes[999], ensuring a systematic and transparent approach in the development of national clinical practice guidelines for the prevention of HIV. Based on the strength of the evidence, this study was used to develop national clinical guidelines on the management of patients on PrEP,[30] and informed the decision of the Irish government to implement a publicly funded PrEP programme nationally for MSM and serodiscordant couples at increased risk, and for other populations on a case-by-case basis as determined by the treating HIV specialist.[31]

Despite the strength of the evidence, however, the present study is subject to a number of limitations. First, there was a lack of data on a number of other high risk groups, such as transgender women (only one study included transgender women, which made up less than 1% of participants[3]) and sex workers (one study included sex workers, however disaggregated data were not reported[17]). Second, adherence was notably poor in most studies that enrolled heterosexual women, limiting conclusions in this group. Additionally, as observational studies were excluded from this review, PrEP effectiveness may be lower in real-world settings in all populations if adherence is suboptimal. Third, while PrEP is considered to have an excellent safety profile, the maximum follow-up period was 6.9 years in this review and, therefore, long-term safety was not assessed.

Fourth, while studies in this review did not detect risk compensation, evidence from placebo-controlled trials is often insufficient to determine its presence. It is not possible to reach conclusions on the impact of PrEP on behaviour when participants do not know if they are taking active PrEP or placebo. However, it is possible to evaluate the impact of the support provided to all participants over time (provision of condoms, counselling on safer

sex practices). Studies generally demonstrated no change or an improvement in safer sex practices. In the open-label PROUD study (where participants knew they were taking PrEP), there was no difference between the immediate and deferred PrEP groups in the total number of sexual partners in the three months prior to the 1-year questionnaire.[6] However, a greater proportion of the immediate group reported receptive anal sex without a condom with 10 or more partners compared with the deferred group. Importantly, there was no difference in the frequency of bacterial STIs between groups, the most reliable proxy for changes in sexual behaviour (as it is not self-reported). Fifth, a number of studies in this review had zero events in one or both arms of the study. Standard meta-analytic approaches typically exclude these trials, resulting in a loss of data. A sensitivity analysis using alternative meta-analytic methods to account for these studies generally found similar findings, with the exception of the estimate of effectiveness in the 'low adherence' MSM group, which was no longer statistically significant.

Finally, the generalisability of studies to other clinical settings should be done with caution. All trials that enrolled heterosexuals were conducted in sub-Saharan Africa, a part of the world with a generalised HIV epidemic and suboptimal antiretroviral coverage. Additionally, the only trial that enrolled PWID was conducted in Bangkok, where needle exchange was unavailable to participants, and investigators could not differentiate sexually from parenterally acquired HIV.

Research in context and implications for practice

HIV infection is of significant public health importance. There were 523 diagnoses of HIV notified in 2018 in Ireland, representing a rate of 11 per 100,000 population, and over half (56%) of all diagnoses were in the MSM group.[32] The rate of HIV in Ireland is high compared

with other countries in Western Europe, many of which have seen declines in their HIV rates in recent years.[1] This highlights the ongoing need for newer, more effective prevention strategies to halt the transmission of HIV.

Our finding of high PrEP effectiveness among MSM concurs with other recent systematic reviews that focussed solely on the MSM population.[33 34] To our knowledge, this systematic review provides the first GRADE assessment of the totality of evidence across all populations that includes more recent trials with high adherence.[5 6] Our GRADE assessment differs significantly from that of Okwundu et al., published in 2012.[35]

Our quantification of the strength of the association between adherence and efficacy through meta-regression highlights the clinical importance of medication adherence support and counselling to prospective PrEP users. Additionally, our finding of emtricitabine resistance mutations occurring almost four times more often in those with acute HIV enrolment has implications for PrEP implementation going forward. Assessing if the patient could be in the 'window period' (the time between exposure to HIV and the point when HIV testing will give an accurate result) at enrolment is of critical importance, to ensure the patient is HIV negative prior to commencing PrEP. This highlights the need for PrEP delivery as part of a monitored programme that incorporates HIV testing and patient counselling on the risk and long-term consequences of resistance if poorly adherent to PrEP.

An additional finding of interest is the lack of significant difference in the effectiveness and safety of single agent tenofovir compared with combined tenofovir/emtricitabine. This may have implications for clinical practice, as tenofovir may be a suitable alternative for emtricitabine-allergic patients, and in resource-poor settings if cost or procurement of combination tenofovir/emtricitabine is an issue.

Conclusions

In conclusion, high-certainty evidence exists that PrEP is safe and, assuming adequate adherence, effectively prevents HIV in MSM and serodiscordant couples. One study found PrEP to be effective in PWID. The uncertainty regarding PrEP effectiveness in heterosexual individuals persists. Clinicians and policy-makers may decide to recommend PrEP to heterosexual individuals on a case-by-case basis, acknowledging adherence-related issues reported in trials. This review emphasises the importance of adherence support to ensure PrEP effectiveness is maintained, as well as the need for frequent HIV testing at enrolment and follow-up to avoid viral drug resistance mutations. Following the conclusion of this study, the Irish government implemented a publicly-funded PrEP programme for all individuals at increased risk of HIV acquisition, and developed national clinical practice guidelines for the provision of PrEP.

Author contributions: Dr. O Murchu: concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of paper for important intellectual content, statistical analysis. Mr. Marshall: acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of paper for important intellectual content. Dr. Teljeur: concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of paper for important intellectual content, statistical analysis, supervision. Dr. Harrington: concept and design, critical revision of paper for important intellectual content, analysis and interpretation of data, drafting of the manuscript, supervision. Dr. Hayes: concept and design, drafting of the manuscript, supervision. Dr. Moran: concept and design, drafting of the manuscript, supervision. Dr.

Ryan: concept and design, critical revision of paper for important intellectual content, drafting of the manuscript, supervision.

Competing interests: None declared.

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data sharing: All data relevant to the study are included in the article or uploaded as supplementary information.

Acknowledgements: The HSE's Sexual Health and Crisis Pregnancy Programme; the Gay Men's Health Centre Dublin; HIV Ireland; Act Up Dublin and the Gay Health Network.

References

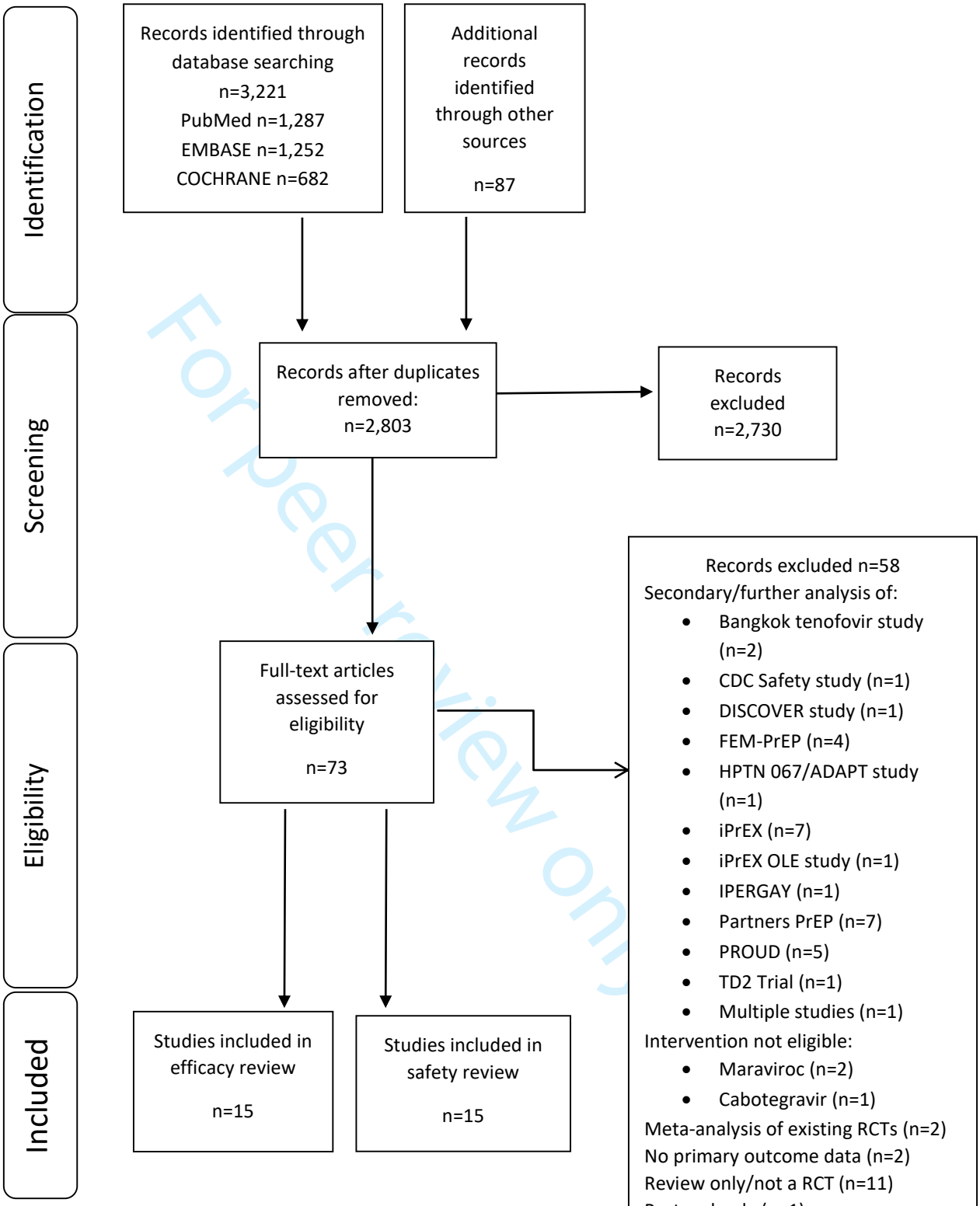
1. UNAIDS. Global HIV & AIDS statistics — 2020 fact sheet. Available at: https://www.unaids.org/en/resources/fact-sheet. Accessed 11.9.2021. 2020 [
2. WHO. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Available at: https://www.who.int/hiv/pub/guidelines/keypopulations/en/. Accessed 22.7.2019. 2014
3. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. 2010; 363(27).
4. WHO. WHO Expands Recommendation On Oral Preexposure Prophylaxis Of Hiv Infection (Prep). Available at: https://apps.who.int/iris/bitstream/handle/10665/197906/WHO_HIV_2015.48_eng.pdf;jsessionid=7B04813AFDE92D7F5EE3D71C8E921BBA?sequence=1. Accessed 22.7.2019. 2015
5. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *The New England journal of medicine* 2015;373(23):2237-46. doi: 10.1056/NEJMoa1506273 [published Online First: 2015/12/02]
6. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet (London, England)* 2016;387(10013):53-60. doi: 10.1016/s0140-6736(15)00056-2 [published Online First: 2015/09/14]
7. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *The New England journal of medicine* 2012;367(5):411-22. doi: 10.1056/NEJMoa1202614 [published Online First: 2012/07/13]
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339 doi: 10.1136/bmj.b2700
9. GRADE. The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) working group. Available at: http://www.gradeworkinggroup.org/.
10. Cochrane. The Cochrane Risk of Bias tool. Cochrane Handbook: Chapter 8. Available at: https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm.
11. Beisemann M, Doebler P, Holling H. Comparison of random-effects meta-analysis models for the relative risk in the case of rare events: A simulation study. *Biom J* 2020;62(7):1597-630. doi: 10.1002/bimj.201900379 [published Online First: 2020/06/09]
12. Chen Y, Hong C, Ning Y, et al. Meta-analysis of studies with bivariate binary outcomes: a marginal beta-binomial model approach. *Stat Med* 2016;35(1):21-40. doi: 10.1002/sim.6620 [published Online First: 2015/08/26]
13. Cheng J, Pullenayegum E, Marshall JK, et al. Impact of including or excluding both-armed zero-event studies on using standard meta-analysis methods for rare event outcome: a simulation study. *BMJ Open* 2016;6(8):e010983. doi: 10.1136/bmjopen-2015-010983
14. Rücker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Stat Med* 2008;27(5):746-63. doi: 10.1002/sim.2971 [published Online First: 2007/06/27]
15. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England)* 2013;381(9883):2083-90. doi: 10.1016/s0140-6736(13)61127-7 [published Online First: 2013/06/19]
16. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *New England journal of medicine* 2012; 367(5).

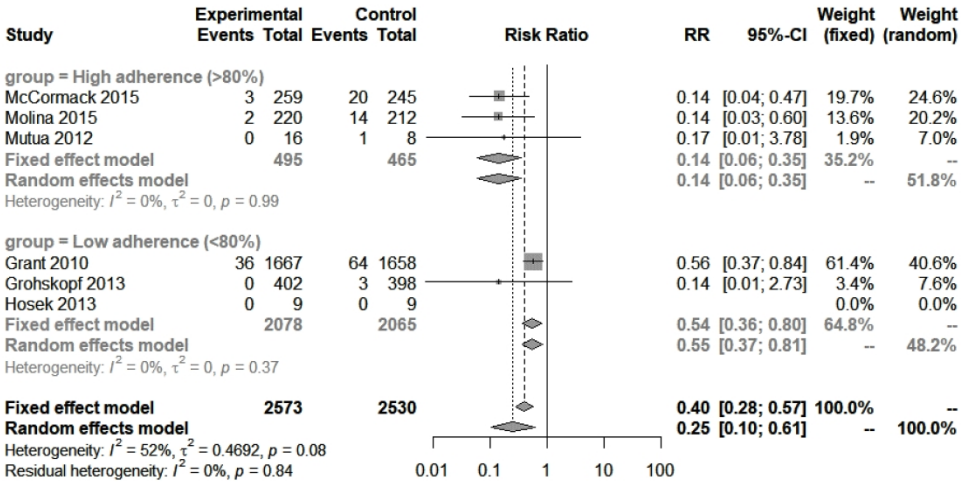
http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/265/CN-00840265/frame.html.
17. Peterson L, Taylor D, Roddy R, et al. Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial. *PLoS Clinical Trials* 2007;2(5):e27. doi: 10.1371/journal.pctr.0020027
18. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *New England journal of medicine* 2012; 367(5). http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/266/CN-00840266/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770474/pdf/nihms493581.pdf.
19. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *The New England journal of medicine* 2015;372(6):509-18. doi: 10.1056/NEJMoa1402269 [published Online First: 2015/02/05]
20. Grohskopf LA, Chillag KL, Gvetadze R, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *Journal of acquired immune deficiency syndromes (1999)* 2013;64(1):79-86. doi: 10.1097/QAI.0b013e31828ece33 [published Online First: 2013/03/08]
21. Mutua G, Sanders E, Mugo P, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. *Plos one* 2012; 7(4). http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/614/CN-00848614/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325227/pdf/pone.0033103.pdf.
22. Kibengo FM, Ruzagira E, Katende D, et al. Safety, adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. *PLoS One* 2013;8(9):e74314. doi: 10.1371/journal.pone.0074314 [published Online First: 2013/10/03]
23. Baeten JM, Donnell D, Mugo NR, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. *The lancet Infectious diseases* 2014; 14(11). http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/639/CN-01053639/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252589/pdf/nihms635147.pdf.
24. Bekker LG, Roux S, Sebastien E, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. *The lancet HIV* 2018;5(2):e68-e78. doi: 10.1016/s2352-3018(17)30156-x [published Online First: 2017/10/08]
25. Hosek SG, Siberry G, Bell M, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. *Journal of acquired immune deficiency syndromes (1999)* 2013;62(4):447-56. doi: 10.1097/QAI.0b013e3182801081 [published Online First: 2013/10/19]
26. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014;14(9):820-9. doi: 10.1016/s1473-3099(14)70847-3 [published Online First: 2014/07/30]
27. Molina JM CI, Spire B et al.,. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV 2017; 4: e402–e410. 2017
28. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-

controlled, phase 3, non-inferiority trial. *Lancet (London, England)* 2020;396(10246):239 - 54. doi: 10.1016/S0140-6736(20)31065-5

29. Ogbuagu O, Ruane PJ, Podzamczer D, et al. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet HIV* 2021;8(7):e397-e407. doi: https://doi.org/10.1016/S2352-3018(21)00071-0
30. Health Service Executive (HSE). Clinical management guidance for individuals taking HIV PrEP within the context of a combination HIV (and STI) prevention approach in Ireland. PrEP clinical management guidance. Version 1.1. October 2019. Available at: https://www.sexualwellbeing.ie/for-professionals/prep-information-for-service-providers/guidelines-for-the-management-of-prep-in-ireland.pdf. Accessed 11.9.2021., 2019.
31. Department of Health. Taoiseach and Ministers for Health announce HIV PrEP programme: Press release. Published on 10 October 2019. 2019 [11.9.2021]. Available from: https://www.gov.ie/en/press-release/taoiseach-and-ministers-for-health-announce-hiv-prep-programme/.
32. Health Protection Surveillance Centre (HPSC). HIV in Ireland, 2018. Annual Epidemiological Report. Available at: https://www.hpsc.ie/a-z/hivandaids/hivdataandreports/HIV_2018_finalrev.pdf. Accessed 11.9.2021. 2019
33. Huang X, Hou J, Song A, et al. Efficacy and Safety of Oral TDF-Based Pre-exposure Prophylaxis for Men Who Have Sex With Men: A Systematic Review and Meta-Analysis. *Frontiers in pharmacology* 2018;9:799. doi: 10.3389/fphar.2018.00799 [published Online First: 2018/09/21]
34. Freeborn K, Portillo CJ. Does pre-exposure prophylaxis for HIV prevention in men who have sex with men change risk behaviour? A systematic review. *J Clin Nurs* 2018;27(17-18):3254-65. doi: 10.1111/jocn.13990
35. Okwundu CI, Uthman OA, Okoromah CAN. Antiretroviral pre - exposure prophylaxis (PrEP) for preventing HIV in high - risk individuals. *Cochrane Database of Systematic Reviews* 2012(7) doi: 10.1002/14651858.CD007189.pub3

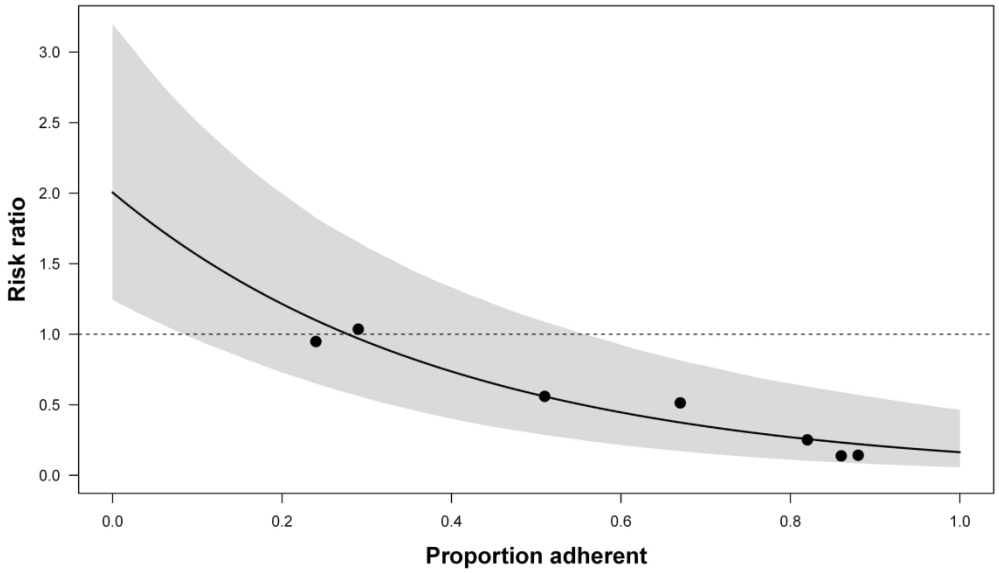
Figure 1. PRISMA diagram of study selection





Forest plot of the meta-analysis of PrEP effectiveness in all MSM trials, PrEP versus placebo or no drug. Subgroups include high (≥80%) adherence and low (<80%) adherence. 'Events' refers to new HIV infections and 'Total' refers to total person-years at risk during the study period.

1055x529mm (118 x 118 DPI)



The X-axis represents the trial-level adherence as a proportion and the Y-axis represents the effectiveness as rate ratios. The solid line represents the fitted regression line and the shaded area the 95% Confidence Interval. Only studies that reported trial plasma drug concentrations contributed to analysis, represented as circles (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), VanDamme 2012 (FEM-PrEP). In the PROUD trial, adherence was only confirmed by plasma drug concentration in patients who reported taking PrEP (88%).

275x159mm (300 x 300 DPI)

Supplementary Material 1: Protocol

1. Background

Human Immunodeficiency Virus (HIV) persists as a significant public health threat. There were 511 HIV notifications in Ireland in 2016, giving a rate of 11.2 per 100,000. This is the highest rate ever reported in Ireland.[1] Men who have sex with men (MSM) remain the population most affected by HIV. In 2015, there were 247 new HIV diagnoses reported among MSM, just over half (51%) of all diagnoses in 2015. The number of diagnoses in 2015 was the highest number ever reported among MSM in Ireland and represents an increase of 34% compared to 2014.[1]

Pre-exposure prophylaxis (PrEP) is a biomedical HIV prevention strategy whereby oral anti-retrovirals (namely tenofovir-emtricitabine, Truvada®) are taken daily by HIV-negative individuals to prevent infection. In their latest guidelines, the World Health Organization (WHO) recommends that PrEP containing tenofovir disoproxil fumarate should be offered as part of HIV prevention programmes to people at 'substantial risk of HIV infection'.[2] Of note, PrEP offers no protection against sexually transmitted infections other than HIV.

In August 2016, the European Commission granted marketing authorisation for once-daily Truvada® in combination with safer-sex practices to reduce the risk of sexually acquired HIV-1 infection among uninfected adults at high risk. Therefore Truvada® is licensed for PrEP in Ireland.[3] However, it has not been made available through the Health Service Executive (HSE); no PrEP programme has been implemented and it is not reimbursed through the Primary Care Reimbursement Scheme.

2. Objective

To perform a systematic review of the efficacy of oral antiretroviral pre-exposure prophylaxis (PrEP) therapy to prevent HIV infection in all populations.

3. Methods

A systematic review of Randomised Controlled Trials (RCTs) will be performed. Systematic review will be registered with PROSPERO.

3.1 Criteria for considering studies for this review

Types of studies

RCTs that evaluated the efficacy of antiretroviral chemoprophylaxis in preventing HIV infection in men who have sex with men (MSM).

Types of participants

All populations at increased risk, including MSM transmission (males who have sex with males), transmission between serodiscordant sexual partners, heterosexual transmission, and people who inject drugs.

Types of interventions

Any oral tenofovir-based PrEP regimen.

Types of comparators

Placebo, no PrEP, or alternative medication/dosing schedule.

Types of outcome measures

Primary outcome:

Incidence of new HIV infections.

Secondary outcomes:

1. Adherence to PrEP (as measured by the primary studies)
2. Adverse events associated with PrEP (frequency and type of adverse effects or complications)
3. New STI infections
4. Behaviour change associated with PrEP administration (number of episodes of condomless anal intercourse and number of new sexual partners).

Table 1 outlines the PICOS criteria for inclusion of studies for inclusion.

Table 1: PICOS criteria

PICOS Criteria: Study Selection	
Population	Males who have sex with males, heterosexuals at increased risk, serodiscordant couples, people who inject drugs
Intervention	Pre-exposure prophylaxis (any oral antiretroviral formulation)
Comparator	Placebo, no treatment or alternative medication/dosage schedule
Outcomes	**Primary outcome:** HIV incidence **Secondary outcomes:** 1. Adherence to PrEP (as measured by the primary studies)

	2. Adverse events associated with PrEP (frequency and type of adverse effects or complications) 3. New STI infections 4. Behaviour change reported in RCTs associated with PrEP administration (episodes of condomless anal intercourse and number of new sexual partners)
Studies	Randomised Controlled Trials

3.2 Search methods for identification of studies

Electronic searches

Electronic searches will be conducted in Medline (PubMed), Embase and the Cochrane Register of Controlled Trials. Additional searches will include the CRD DARE Database, Morbidity and Mortality Weekly Report (CDC), Eurosurveillance reports and hand-searching of journals. The WHO International Clinical Trials Registry Platform and ClinicalTrials.gov will be searched for ongoing or prospective trials.

No restrictions will be placed based on location of the intervention. No language restrictions will be used. Articles in languages other than English will be translated where necessary.

The detailed search strategies for each of the databases MEDLINE via PubMed, EMBASE and The Cochrane Central Register of Controlled Trials are as follows:

Table 2: PubMed search strategy

PubMed Search	Queries
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR HIV[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR HIV infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]
#2	Search pre-exposure prophylaxis[tiab] OR preexposure prophylaxis[tiab] OR PREP[tiab] OR anti-retroviral chemoprophylaxis[tiab] OR antiretroviral chemoprophylaxis[tiab] OR chemoprevention[mh] OR chemoprevention[tiab] OR HIV prophylaxis[tiab]
#3	Search tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil
#4	#2 OR #3
#5	#1 AND #4 AND Filters: Clinical Trial, Randomized Controlled Trial, from 1000/1/1 - 2020/7/5

Table 3: Cochrane Central register search strategy

ID	Search
#1	MeSH descriptor HIV Infections explode all trees

#2	MeSH descriptor HIV explode all trees
#3	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME
#4	MeSH descriptor Sexually Transmitted Diseases, Viral, this term only
#5	(#1 OR #2 OR #3 OR #4)
#6	MeSH descriptor Chemoprevention explode all trees
#7	pre-exposure prophylaxis:ti,ab,kw OR preexposure prophylaxis:ti,ab,w OR PREP:ti,ab,kw OR anti-retroviral chemoprophylaxis:ti,ab,kw OR antiretroviral chemoprophylaxis:ti,ab,kw OR hiv prophylaxis:ti,ab,kw
#8	(#6 OR #7)
#9	tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil
#10	(#8 OR #9)
#11	(#5 AND #10)

Table 4: Embase search strategy

No.	Query
#1	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection'/de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus'/de OR 'human immunodeficiency virus' OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab OR 'human immunedeficiency virus':ti OR 'human immunedeficiency virus':ab OR 'human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab OR 'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab OR 'acquired immunedeficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab
#2	random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over*:ti OR cross?over:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/de OR 'crossover procedure' OR 'double-blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/de OR 'single-blind procedure' OR 'randomised controlled trial'/de OR 'randomised controlled trial' OR allocat*:ti OR allocat*:ab
#3	'pre-exposure prophylaxis' OR 'preexposure prophylaxis' OR prep OR 'anti-retroviral chemoprophylaxis' OR 'antiretroviral chemoprophylaxis' OR 'chemoprevention'/syn OR 'hiv prophylaxis' OR 'chemoprophylaxis'/syn
#4	'tenofovir'/syn OR tnf OR Tenofovir OR 'pmpa'/syn OR 'viread'/syn OR 'emtricitabine'/syn OR emc OR 'truvada'/syn OR 'emtriva'/syn OR 'coviracil'/syn
#5	#3 OR #4
#6	#1 AND #2 AND #5

Searching other resources

The reference lists of all included studies will be also be searched.

3.3 Data collection

Two reviewers will independently read the titles, abstracts, and descriptor terms of the search output from the different databases to identify potentially eligible studies. Full text articles will be obtained for all citations identified as potentially eligible. Both reviewers will independently inspect these to establish the relevance of the articles according to the pre-specified criteria. Studies will be reviewed for relevance based on study design, types of participants, interventions, and outcome measures. Reasons for excluding potentially relevant studies will be provided in an excluded studies table.

3.4 Data extraction and management

Data will be independently extracted using an agreed pro forma. Both reviewers will verify the extracted data. Extracted information will include the following:

- Study details: citation, study design and setting, time period and source of funding.
- Participant details: study population demographics, risk characteristics, population size and attrition rate.
- Intervention details: type of drug, comparator, dose, duration and route of administration.
- Outcome details: incidence of HIV infection (including type of laboratory tests used to confirm HIV diagnosis before and after administering PrEP), degree of adherence to PrEP, adverse effects, other STI infections.

RevMan software will be used to record extracted data. The reviewers will independently extract the data and enter them into RevMan; all entries will be rechecked by both reviewers, and all disagreements will be resolved by discussion. If results are pooled, a random effects meta-analysis, using the Mantel-Haenzel rate ratio, will be employed. Table 5 summarises the data collection, management and analysis.

Table 5: Data Collection, Management & Analysis

Data Collection and Management

Selection of studies	• Citations will be screened by one reviewer to eliminate clearly irrelevant studies • Two people will independently review the remaining citations per the inclusion criteria • Any disagreements will be resolved by discussion, or if necessary a third reviewer
Data extraction and management	• Data extraction will be performed independently onto a data extraction pro forma by two people • Any disagreements will be resolved by discussion or a third reviewer • RevMan software will be used to record extracted data
Assessment of risk of bias in included studies	• Risk of bias will be assessed using the Cochrane Risk of Bias Tool for RCTs • This will be performed by two people independently, with any disagreement being resolved by discussion or a third party • Small study bias will be assessed using a funnel plot and Egger's test • An overall assessment of the quality of the evidence will be assessed using the GRADE approach†
Measures of treatment effect and data synthesis	• Effect sizes will be expressed as the reduction in relative risk (RR) of HIV infection in the treatment group compared to control • A meta-analysis will be performed to provide a pooled risk if there is sufficient homogeneity across studies (all statistical analysis will be performed in R) • If significant heterogeneity is observed, a narrative metasynthesis will be performed.
Assessment of heterogeneity	• Clinical heterogeneity will be assessed by the reviewers based on the description of the interventions in the RCTs • Statistical heterogeneity will be examined using the I^2 statistic.

†The Cochrane Handbook. Section 12.2.1: The GRADE approach. Available at: http://handbook.cochrane.org/chapter_12/12_2_1_the_grade_approach.htm. Accessed May 2017.

3.5 Assessment of risk of bias in included studies

Two reviewers will independently examine the components of each included trial for risk of bias using a standard form. The Cochrane Risk of Bias tool will be employed. This will include information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the studies will be assessed and classified as adequate, inadequate or unclear as per the Cochrane Handbook of Systematic Reviews of Interventions. Where differences arise, they will be resolved by discussions with the third reviewer.

Table 6 outlines the potential risks of bias that will be assessed in included studies.

Table 6: Risk of Bias

Risk of Bias

Sequence generation	• Adequate: investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelope shuffling, etc. • Inadequate: investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number. • Unclear: insufficient information to permit judgement of the sequence generation process.
Allocation concealment	• Adequate: participants and the investigators enrolling participants cannot foresee assignment (e.g. central allocation; or sequentially numbered, opaque, sealed envelopes). • Inadequate: participants and investigators enrolling participants can foresee upcoming assignment (e.g. an open random allocation schedule (e.g. a list of random numbers); or envelopes were unsealed or nonopaque or not sequentially numbered). • Unclear: insufficient information to permit judgement of the allocation concealment or the method not described
Blinding	• Adequate: blinding of the participants, key study personnel and outcome assessor, and unlikely that the blinding could have been broken. Or lack of blinding unlikely to introduce bias. No blinding in the situation where non-blinding is not likely to introduce bias. • Inadequate: no blinding, incomplete blinding and the outcome is likely to be influenced by lack of blinding. • Unclear: insufficient information to permit judgement of adequacy or otherwise of the blinding.
Incomplete outcome data	• Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups. • Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data. • Unclear: insufficient reporting of attrition or exclusions.
Selective Reporting	• Adequate: a protocol is available which clearly states the primary outcome as the same as in the final trial report. • Inadequate: the primary outcome differs between the protocol and final trial report. • Unclear: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.
Other sources of bias	• Adequate: there is no evidence of bias from other sources. • Inadequate: there is potential bias present from other sources (e.g. early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design).

An overall assessment of the quality of the evidence will be assessed using the GRADE approach (the Cochrane Handbook, Section 12.2.1: The GRADE approach).

3.6 Measures of treatment effect

Outcome measures for dichotomous data (e.g., rate of HIV infection comparing intervention and comparator groups) will be calculated as a rate ratio (RR) with 95% confidence intervals (CI). A meta-analysis will be performed to provide a pooled risk if there is sufficient homogeneity across studies (all statistical analysis will be performed in Review Manager and R).

3.7 Dealing with missing data

Study authors will be contacted to provide further information on the results.

3.8 Assessment of heterogeneity

Clinical heterogeneity will be assessed by the reviewers based on the description of the interventions in the RCTs. Statistical heterogeneity will be examined using the I^2 statistic.

3.9 Subgroup analysis

Subgroup analyses by population group and adherence will be performed in the estimation of effectiveness.

3.10 Reporting guidelines

Reporting will adhere to the PRISMA guidelines for systematic reviews.[6]

References

1. HIV in Ireland 2016 Report. HPSC, HSE and UCD. Available at: https://www.hpsc.ie/a-z/hivandaids/hivdataandreports/2016reports/HIVIreland_2016.pdf.

2. WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015. Available at: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf. Accessed May 2017.

3. Truvada: EPAR. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/truvada

4. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339 doi: 10.1136/bmj.b2700

Supplementary Material 2

Database search – PubMed search strategy

PubMed

Search	Most Recent Queries	Citations
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR HIV[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR HIV infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]	413,629
#2	Search pre-exposure prophylaxis[tiab] OR preexposure prophylaxis[tiab] OR PREP[tiab] OR anti-retroviral chemoprophylaxis[tiab] OR antiretroviral chemoprophylaxis[tiab] OR chemoprevention[mh] OR chemoprevention[tiab] OR HIV prophylaxis[tiab]	35,711
#3	Search tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil	189,421
#4	#2 OR #3	224,005
#5	#1 AND #4 AND Filters: Clinical Trial, Randomized Controlled Trial, from 1000/1/1 - 2020/7/5	1,287

Supplementary Material 3: Additional Results

S3.1 List of included and excluded studies (with reasons)

S3.2 Risk of Bias assessment

S3.3 Funnel plot (all studies)

S3.4 Additional figures and forest plots

S3.5 Results from Thigpen 2012 (by gender)

S3.6 Adherence

S3.7 Change in sexual behaviour/STI rates

S3.1

List of studies included in review

1. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. New England journal of medicine [Internet]. 2012; 367(5):[399-410 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/266/CN-00840266/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770474/pdf/nihms493581.pdf.

2. Baeten JM, Heffron R, Kidoguchi L, Mugo NR, Katabira E, Bukusi EA, et al. Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1–serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda. PLOS Medicine. 2016;13(8):e1002099.

3. Bekker LG, Roux S, Sebastien E, Yola N, Amico KR, Hughes JP, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. The lancet HIV. 2018;5(2):e68-e78.

4. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet (London, England). 2013;381(9883):2083-90.

5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New England journal of medicine [Internet]. 2010; 363(27):[2587-99 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/306/CN-00771306/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079639/pdf/nihms264954.pdf.

6. Grohskopf LA, Chillag KL, Gvetadze R, Liu AY, Thompson M, Mayer KH, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. Journal of acquired immune deficiency syndromes (1999). 2013;64(1):79-86.

7. Hosek SG, Siberry G, Bell M, Lally M, Kapogiannis B, Green K, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. Journal of acquired immune deficiency syndromes (1999). 2013;62(4):447-56.

8. Kibengo FM, Ruzagira E, Katende D, Bwanika AN, Bahemuka U, Haberer JE, et al. Safety,

adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. PLoS One. 2013;8(9):e74314.

9. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2015;372(6):509-18.

10. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet (London, England). 2016;387(10013):53-60.

11. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. The New England journal of medicine. 2015;373(23):2237-46.

12. Mutua G, Sanders E, Mugo P, Anzala O, Haberer JE, Bangsberg D, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. Plos one [Internet]. 2012; 7(4):[e33103 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/614/CN-00848614/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325227/pdf/pone.0033103.pdf.

13. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial. PLoS Clinical Trials. 2007;2(5):e27.

14. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. New England journal of medicine [Internet]. 2012; 367(5):[423-34 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/265/CN-00840265/frame.html.

15. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2012;367(5):411-22.

Supplementary Material

List of studies excluded from review

1. Agot K, Taylor D, Corneli AL, Wang M, Ambia J, Kashuba AD, et al. Accuracy of Self-Report and Pill-Count Measures of Adherence in the FEM-PrEP Clinical Trial: Implications for Future HIV-Prevention Trials. AIDS and behavior. 2015;19(5):743-51. [reason: secondary analysis of FEM-PrEP]

2. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Science translational medicine. 2012;4(151):151ra25. [reason: secondary analysis of iPrEX]

3. Baeten JM, Donnell D, Mugo NR, Ndase P, Thomas KK, Campbell JD, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. The lancet Infectious diseases [Internet]. 2014; 14(11):[1055-64 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/639/CN-01053639/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252589/pdf/nihms635147.pdf. [reason: duplicate]

4. Buchbinder SP, Glidden DV, Liu AY, McMahan V, Guanira JV, Mayer KH, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. The Lancet Infectious diseases. 2014;14(6):468-75. [reason: secondary analysis of iPrEX]

5. Buchbinder SP, Liu AY. CROI 2014: New tools to track the epidemic and prevent HIV infections. Topics in Antiviral Medicine. 2014;22(2):579-93. [reason: review; not a RCT]

6. Campbell JD, Herbst JH, Koppenhaver RT, Smith DK. Antiretroviral prophylaxis for sexual and injection drug use acquisition of HIV. American Journal of Preventive Medicine. 2013;44(1 SUPPL. 2):S63-S9. [reason: review, not a RCT]

7. Celum C, Baeten JM. Antiretroviral-based HIV-1 prevention: Antiretroviral treatment and pre-exposure prophylaxis. Antiviral Therapy. 2012;17(8):1483-93. [reason: review/not a RCT]

8. Corneli AL, Deese J, Wang M, Taylor D, Ahmed K, Agot K, et al. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. Journal of acquired immune deficiency syndromes (1999). 2014;66(3):324-31. [reason: secondary analysis of FEM-PrEP]

9. Corneli AL, McKenna K, Headley J, Ahmed K, Odhiambo J, Skhosana J, et al. A descriptive analysis of perceptions of HIV risk and worry about acquiring HIV among FEM-PrEP

participants who seroconverted in Bondo, Kenya, and Pretoria, South Africa. Journal of the International AIDS Society. 2014;17(3). [reason: secondary analysis of FEM-PrEP]

10. Deutsch MB, Glidden DV, Sevelius J, Keatley J, McMahan V, Guanira J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. The lancet HIV. 2015;2(12):e512-9. [reason: secondary analysis of iPrEX]

11. Dolling DI, Desai M, McOwan A, Gilson R, Clarke A, Fisher M, et al. An analysis of baseline data from the PROUD study: An open-label randomised trial of pre-exposure prophylaxis. Trials. 2016;17(1). [reason: secondary analysis of PROUD]

12. Dunn DT, Glidden DV. Statistical issues in trials of preexposure prophylaxis. Current Opinion in HIV and AIDS. 2016;11(1):116-21. [reason: review/not a RCT]

13. Elbirt D, Mahlab-Guri K, Bezalel-Rosenberg S, Asher I, Sthoeger Z. Pre-exposure prophylaxis as a method for prevention of human immunodeficiency virus infection. Israel Medical Association Journal. 2016;18(5):294-8. [reason: review, not a RCT]

14. Fidler S, Bock P. Prophylactic antiretroviral HIV therapy prevents infection in heterosexual men and women. Evidence-Based Medicine. 2013;18(5):184-5. [Reason: not a RCT, review of Baeten et al.]

15. Gilmore HJ, Liu A, Koester KA, Amico KR, McMahan V, Goicochea P, et al. Participant experiences and facilitators and barriers to pill use among men who have sex with men in the iPrEx pre-exposure prophylaxis trial in San Francisco. AIDS patient care and stds [Internet]. 2013; 27(10):[560-6 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/551/CN-00962551/frame.html. [reason: secondary analysis of iPrEX]

16. Grangeiro A, Couto MT, Peres MF, Luiz O, Zucchi EM, de Castilho EA, et al. Pre-exposure and postexposure prophylaxes and the combination HIV prevention methods (The Combine! Study): protocol for a pragmatic clinical trial at public healthcare clinics in Brazil. BMJ open. 2015;5(8):e009021. [reason: protocol]

17. Grant RM, Liegler T, Defechereux P, Kashuba AD, Taylor D, Abdel-Mohsen M, et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women. AIDS (London, England). 2015;29(3):331-7. [reason: not an efficacy RCT; further analysis of FEM-PrEP]

18. Gray RH, Wawer MJ. Infection in 2012: Mixed results of pre-exposure prophylaxis for HIV prevention. Nature Reviews Urology. 2013;10(2):74-5. [reason: review]

19. Gulick RM, Wilkin TJ, Chen YQ, Landovitz RJ, Amico KR, Young AM, et al. Phase 2 Study of the Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV

Infection in Men Who Have Sex With Men (HPTN 069/ACTG A5305). The Journal of infectious diseases. 2017;215(2):238-46. [reason: different intervention (maraviroc)]

20. Gulick RM, Wilkin TJ, Chen YQ, Landovitz RJ, Amico KR, Young AM, et al. Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV Infection in Women: A Phase 2 Randomized Trial. Annals of internal medicine. 2017;167(6):384-93. [reason: different intervention (maraviroc)]

21. Gust DA, Soud F, Hardnett FP, Malotte CK, Rose C, Kebaabetswe P, et al. Evaluation of Sexual Risk Behavior Among Study Participants in the TENOFOVIR2 PrEP Study Among Heterosexual Adults in Botswana. Journal of acquired immune deficiency syndromes (1999). 2016;73(5):556-63. [reason: secondary analysis of TD2 trial]

22. Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, et al. Adherence to Antiretroviral Prophylaxis for HIV Prevention: A Substudy Cohort within a Clinical Trial of serodiscordant Couples in East Africa. PLoS Medicine. 2013;10(9). [reason: secondary analysis of Partners PrEP]

23. Hanscom B, Janes HE, Guarino PD, Huang Y, Brown ER, Chen YQ, et al. Brief report: Preventing HIV-1 infection in women using oral preexposure prophylaxis: A meta-analysis of current evidence. Journal of Acquired Immune Deficiency Syndromes. 2016;73(5):606-8. [reason: meta-analysis of RCTs]

24. Jiang J, Yang X, Ye L, Zhou B, Ning C, Huang J, et al. Pre-exposure prophylaxis for the prevention of HIV infection in high risk populations: A meta-analysis of randomized controlled trials. PLoS ONE. 2014;9(2). [reason: meta-analysis of existing RCTs]

25. K RA, McMahan V, Goicochea P, Vargas L, Marcus JL, Grant RM, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. AIDS and behavior. 2012;16(5):1243-59. [reason: secondary analysis of iPrEX]

26. Koester KA, Liu A, Eden C, Amico KR, McMahan V, Goicochea P, et al. Acceptability of drug detection monitoring among participants in an open-label pre-exposure prophylaxis study. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2015;27(10):1199-204. [reason: observational study on subset of iPrEX OLE study]

27. Koss CA, Bacchetti P, Hillier SL, Livant E, Horng H, Mgodi N, et al. Differences in Cumulative Exposure and Adherence to Tenofovir in the VOICE, iPrEx OLE, and PrEP Demo Studies as Determined via Hair Concentrations. AIDS Research and Human Retroviruses. 2017;33(8):778-83. [reason: secondary analysis of 3 studies]

28. Lehman DA, Baeten JM, McCoy CO, Weis JF, Peterson D, Mbara G, et al. Risk of drug resistance among persons acquiring HIV within a randomized clinical trial of single-or

dual-agent preexposure prophylaxis. Journal of Infectious Diseases. 2015;211(8):1211-8. [reason: secondary analysis of Partners PrEP study]

29. Liu A, Glidden DV, Anderson PL, Amico KR, McMahan V, Mehrotra M, et al. Patterns and correlates of PrEP drug detection among MSM and transgender women in the global iPrEx study. Journal of Acquired Immune Deficiency Syndromes. 2014;67(5):528-37. [reason: secondary analysis of iPrEX]

30. Liu AY, Vittinghoff E, Chillag K, Mayer K, Thompson M, Grohskopf L, et al. Sexual risk behavior among HIV-uninfected men who have sex with men participating in a tenofovir preexposure prophylaxis randomized trial in the United States. Journal of acquired immune deficiency syndromes (1999). 2013;64(1):87-94. [reason: secondary analysis of US CDC Safety Study]

31. Lorente N, Fugon L, Carrieri MP, Andreo C, Le Gall JM, Cook E, et al. Acceptability of an on-demand pre-exposure HIV prophylaxis trial among men who have sex with men living in France. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2012;24(4):468-77. [reason: acceptability study prior to RCT]

32. Markowitz M, Frank I, Grant RM, Mayer KH, Elion R, Goldstein D, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. The lancet HIV. 2017;4(8):e331-e40. [reason: intervention different (cabotegravir)]

33. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Chuachoowong R, Mock PA, et al. Enrollment characteristics and risk behaviors of injection drug users participating in the Bangkok Tenofovir Study, Thailand. PLoS One. 2011;6(9):e25127. [reason: secondary analysis of Bangkok tenofovir study enrolment characteristics]

34. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Risk behaviors and risk factors for HIV infection among participants in the Bangkok tenofovir study, an HIV pre-exposure prophylaxis trial among people who inject drugs. PLoS One. 2014;9(3):e92809. [reason: secondary analysis of Bangkok tenofovir study enrolment characteristics]

35. McCormack SM, Noseda V, Molina JM. PrEP in Europe - Expectations, opportunities and barriers. Journal of the International AIDS Society. 2016;19. [reason: not a RCT; review article]

36. Mehrotra ML, Westreich D, McMahan VM, Glymour MM, Geng E, Grant RM, et al. Baseline Characteristics Explain Differences in Effectiveness of Randomization to Daily Oral TDF/FTC PrEP Between Transgender Women and Cisgender Men Who Have Sex With Men in the iPrEx Trial. Journal of acquired immune deficiency syndromes (1999).

2019;81(3):e94-e8. Epub 2019/06/14. doi: 10.1097/qai.0000000000002037. [reason: secondary analysis iPrEX]

37. Mills A, Workowski K, Campbell T, Benson P, Crofoot G, Salazar L, et al. Renal outcomes for participants taking F/TAF vs. F/TDF for HIV PrEP in the DISCOVER trial. Open Forum Infectious Diseases. 2019;6:S64. doi: 10.1093/ofid/ofz359.139. [reason: review; no efficacy data]

38. Miltz AR, Lampe FC, Bacchus LJ, McCormack S, Dunn D, White E, et al. Intimate partner violence, depression, and sexual behaviour among gay, bisexual and other men who have sex with men in the PROUD trial. BMC public health. 2019;19(1):431. Epub 2019/04/27. doi: 10.1186/s12889-019-6757-6.. [reason: secondary analysis PROUD]

39. Mugwanya KK, Donnell D, Celum C, Thomas KK, Ndase P, Mugo N, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis. The lancet Infectious diseases [Internet]. 2013; 13(12):[1021-8 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/297/CN-00915297/frame.html. [reason: longitudinal analysis of Partners PrEP]

40. Mujugira A, Baeten JM, Donnell D, Ndase P, Mugo NR, Barnes L, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. Plos one [Internet]. 2011; 6(10):[e25828 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/232/CN-00805232/frame.html. [reason: secondary analysis Partners PrEP]

41. Murnane PM, Brown ER, Donnell D, Coley RY, Mugo N, Mujugira A, et al. Estimating Efficacy in a Randomized Trial With Product Nonadherence: Application of Multiple Methods to a Trial of Preexposure Prophylaxis for HIV Prevention. American Journal of Epidemiology. 2015;182(10):848-56. [reason: secondary analysis Partners PrEP]

42. Murnane PM, Celum C, Mugo N, Campbell JD, Donnell D, Bukusi E, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS (london, england) [Internet]. 2013; 27(13):[2155-60 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/174/CN-01000174/frame.html. [reason: secondary analysis Partners PrEP]

43. Ndase P, Celum C, Campbell J, Bukusi E, Kiarie J, Katabira E, et al. Successful discontinuation of the placebo arm and provision of an effective HIV prevention product after a positive interim efficacy result: the partners PrEP study experience. Journal of acquired immune deficiency syndromes (1999) [Internet]. 2014; 66(2):[206-12 pp.]. Available from: http://cochranelibrary-

wiley.com/o/cochrane/clcentral/articles/717/CN-00992717/frame.html. [reason: review of Partners PrEP]

44. O'Halloran C, Rice B, White E, Desai M, D TD, McCormack S, et al. Chemsex is not a barrier to self-reported daily PrEP adherence among PROUD study participants. International Journal of Drug Policy. 2019;74:246-54. doi: 10.1016/j.drugpo.2019.10.007 [reason: secondary analysis PROUD]

45. Page K, Tsui J, Maher L, Choopanya K, Vanichseni S, Philip Mock M, et al. Biomedical HIV prevention including pre-exposure prophylaxis and opiate agonist therapy for women who inject drugs: State of research and future directions. Journal of Acquired Immune Deficiency Syndromes. 2015;69:S169-S75. [reason: review; not a RCT]

46. Post F, Spinner C, Coll P, Hawkins T, Anderson J, Zhong L, et al. DISCOVER in Europe: A sub-analysis of the phase 3 randomized, controlled trial of daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP). HIV Medicine. 2019;20:243-4. doi: 10.1111/hiv.12815. [reason: abstract only/no full text available]

47. Roux P, Fressard L, Suzan-Monti M, Chas J, Sagaon-Teyssier L, Capitant C, et al. Is on-Demand HIV Pre-exposure Prophylaxis a Suitable Tool for Men Who Have Sex With Men Who Practice Chemsex? Results From a Substudy of the ANRS-IPERGAY Trial. Journal of acquired immune deficiency syndromes (1999). 2018;79(2):e69-e75. Epub 2018/09/14. doi: 10.1097/qai.0000000000001781. [reason: secondary analysis IPERGAY]

48. Ruane PJ, Clarke A, Post FA, Schembri G, Jessen H, Trottier B, et al. Phase 3 randomized, controlled DISCOVER study of daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP): Week 96 results. HIV Medicine. 2019;20:95-6. doi: 10.1111/hiv.12815. [reason: abstract only/no full text available]

49. Sacks HS. Preexposure tenofovir-emtricitabine reduced HIV infection in men who have unprotected anal sex with men. Annals of Internal Medicine. 2016;164(2):JC3. [reason: review of PROUD]

50. Spinner CD, Brunetta J, Shalit P, Prins M, Cespedes M, Brainard D, et al. DISCOVER study for HIV pre-exposure prophylaxis (PrEP): F/TAF has a more rapid onset and longer sustained duration of HIV protection compared with F/TDF. Journal of the International AIDS Society. 2019;22. doi: 10.1002/jia2.25327. [reason: abstract only/no full text available]

51. Thomson KA, Baeten JM, Mugo NR, Bekker LG, Celum CL, Heffron R. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. Current Opinion in HIV and AIDS. 2016;11(1):18-26. [reason: review; not a RCT]

52. Velloza J, Bacchetti P, Hendrix CW, Murnane P, Hughes JP, Li M, et al. Short- and Long-Term Pharmacologic Measures of HIV Pre-exposure Prophylaxis Use Among High-Risk Men Who Have Sex With Men in HPTN 067/ADAPT. Journal of acquired immune deficiency syndromes (1999). 2019;82(2):149-58. Epub 2019/07/25. doi: 10.1097/qai.0000000000002128. [reason: secondary analysis HPTN 067/ADAPT]

53. Vermund SH. Safety and tolerability of tenofovir for preexposure prophylaxis among men who have sex with men. Journal of Acquired Immune Deficiency Syndromes. 2013;64(1):3-6. [reason: review; not a RCT]

54. White E, Dunn DT, Desai M, Gafos M, Kirwan P, Sullivan AK, et al. Predictive factors for HIV infection among men who have sex with men and who are seeking PrEP: a secondary analysis of the PROUD trial. Sexually transmitted infections. 2019;95(6):449-54. Epub 2019/03/29. doi: 10.1136/sextrans-2018-053808.. [reason: secondary analysis PROUD]

55. Wohl D, Ruane P, Hosek S, Creticos C, Morris S, Phoenix J, et al. Bone safety outcomes with F/TAF vs. F/TDF for PrEP in the DISCOVER trial. Open Forum Infectious Diseases. 2019;6:S464. doi: 10.1093/ofid/ofz360.1151. [reason: review; no efficacy data]

56. Yacoub R, Nadkarni GN, Weikum D, Konstantinidis I, Boueilh A, Grant RM, et al. Elevations in serum creatinine with tenofovir-based HIV pre-exposure prophylaxis: A meta-analysis of randomized placebo-controlled trials. Journal of Acquired Immune Deficiency Syndromes. 2016;71(4):e115-e8. [reason: meta-analysis of RCTs]

S3.2

Risk of Bias assessment

Two studies were open-label trials and, as such, blinding of participants or investigators was not possible. A further three studies were placebo-controlled trials that additionally investigated alternate dosing schedules; while participants and investigators were blinded to drug assignment, they could not be blinded to regimen assignment. One study contained a 'no pill' arm that could not be blinded in addition to a placebo arm. Two studies had unclear risk for reporting bias due to the fact that study protocols were not available. Figure S1 represents the review authors' judgements about each risk of bias item for each included study.

Figure S1. Risk of bias summary

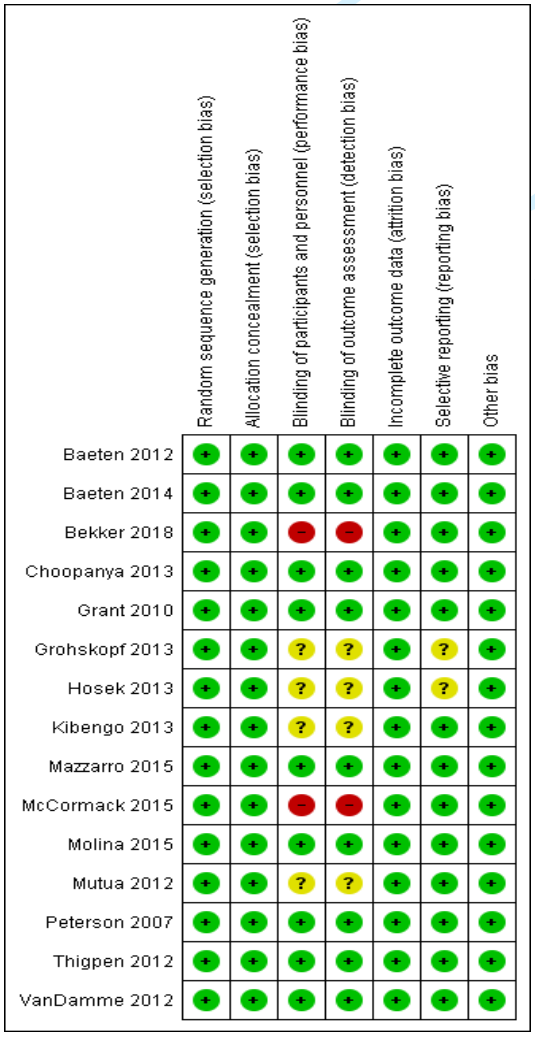
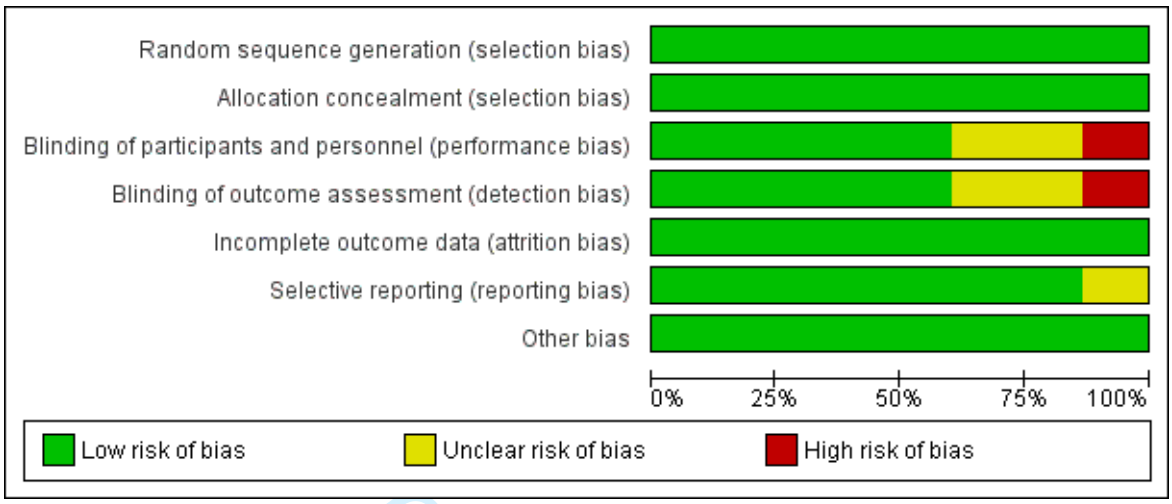
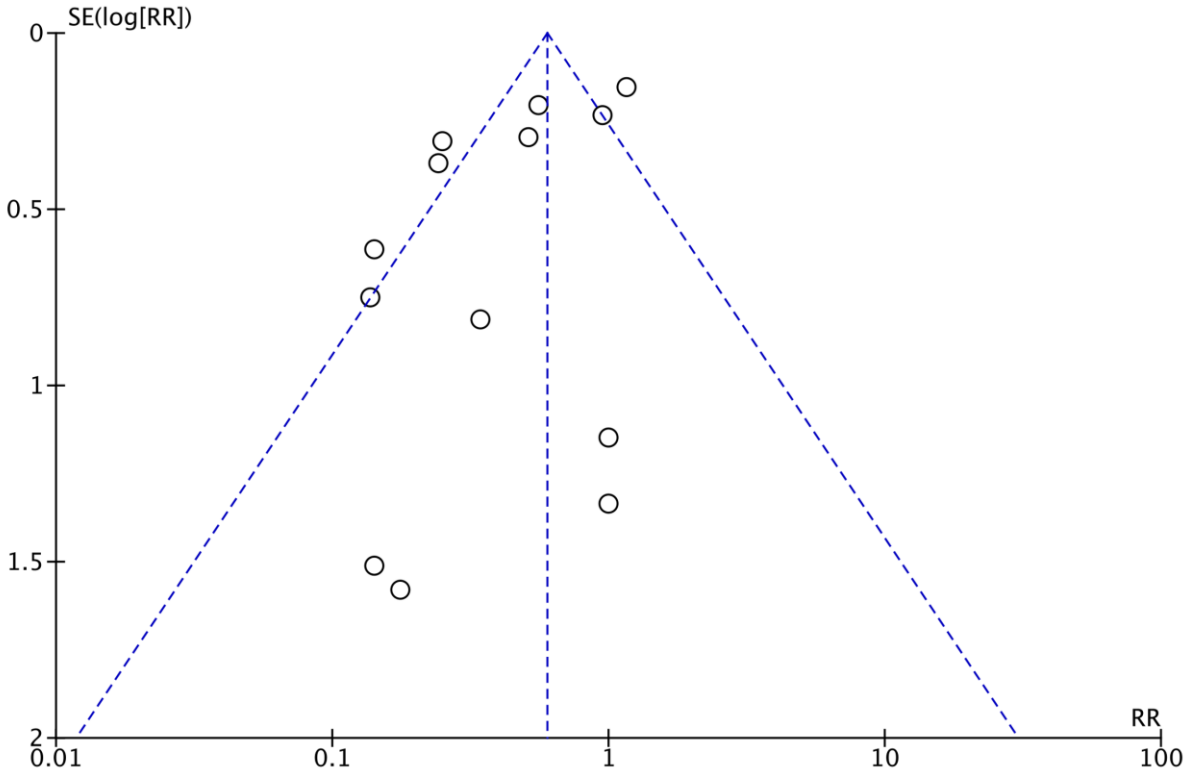


Figure S2 represents the review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure S2. Risk of bias graph



S3.3 Funnel plot (all studies)



A funnel plot of all studies (n=13) is presented. There is no evidence of significant small study bias.

S3.4 Additional figures and forest plots

Efficacy

Figure S3. Meta-analysis: HIV acquisition, all trials (PrEP versus placebo or no drug)

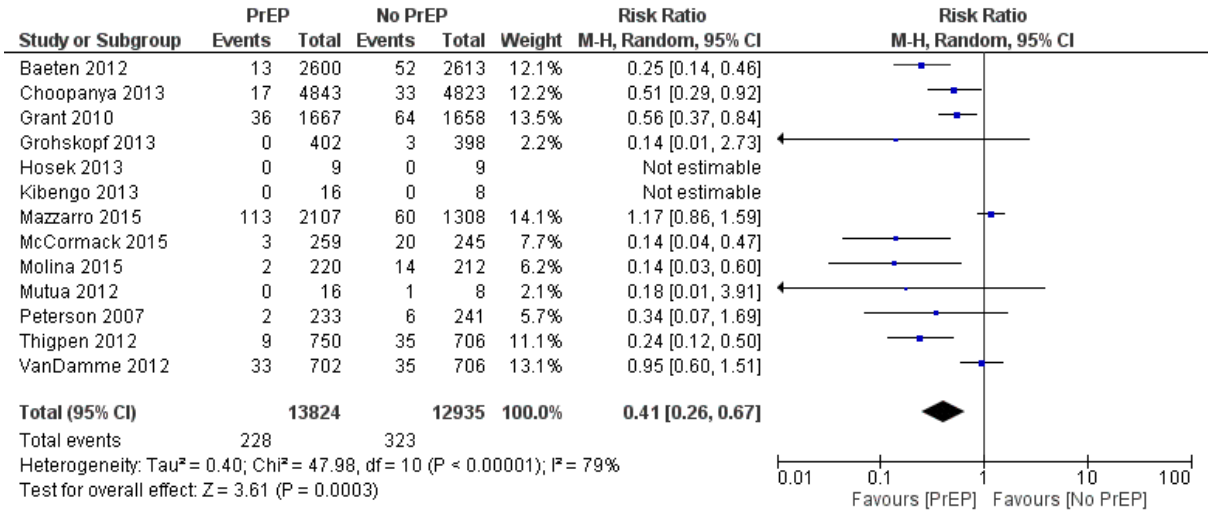


Figure S4. Meta-analysis: HIV acquisition in heterosexual participants, PrEP versus placebo, all trials

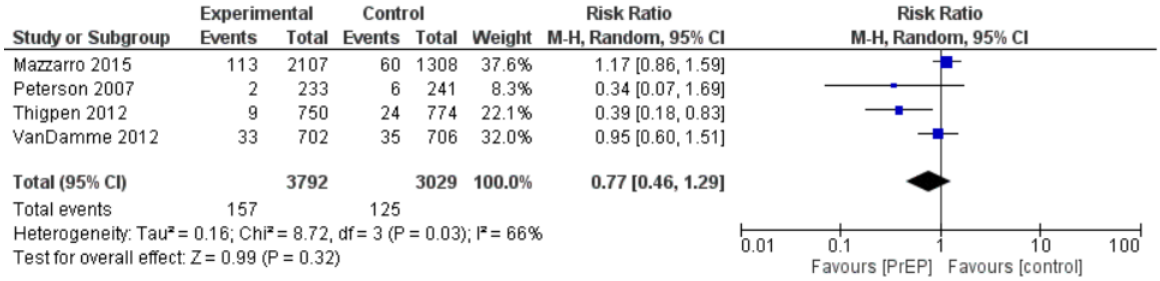
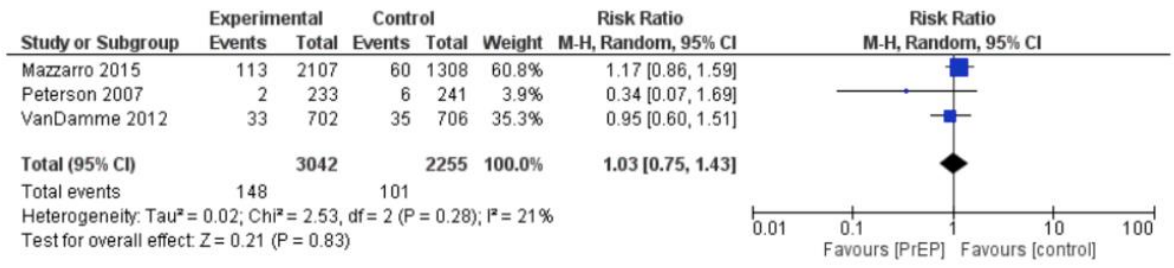


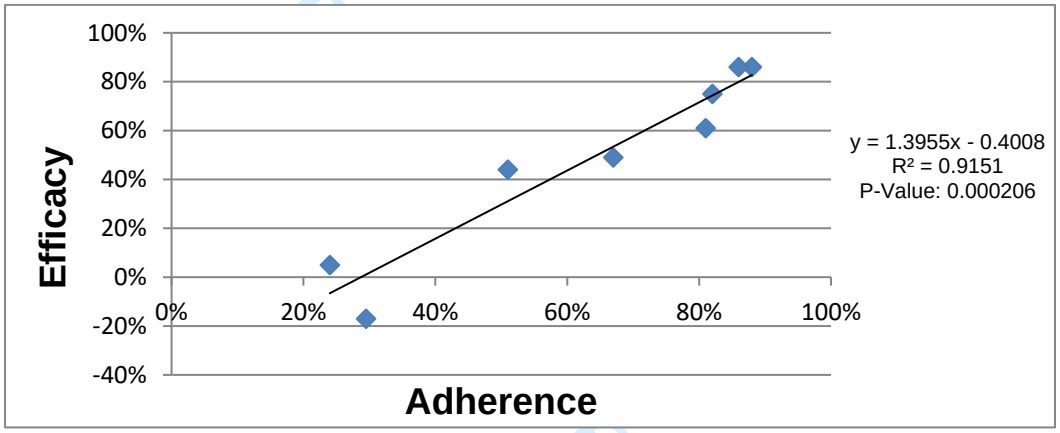
Figure S5. Meta-analysis: HIV acquisition in heterosexual participants, PrEP versus placebo, studies with low (<80%) adherence



Adherence

Figure S3 compares efficacy and adherence (measured by plasma drug concentration of participants, or plasma drug confirmation of self-reported adherence; n=7 trials). A regression model yielded a R^2 of 0.92 ($p<0.001$).

Figure S6. Efficacy as a function of adherence



Caption: Only trials that reported plasma drug concentrations contributed to anlaysis: (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), Thigpen 2012 (TDF2 study), VanDamme 2012 (FEM-PrEP)

Safety

Figure S7. Meta-analysis: 'any adverse event', PrEP versus placebo

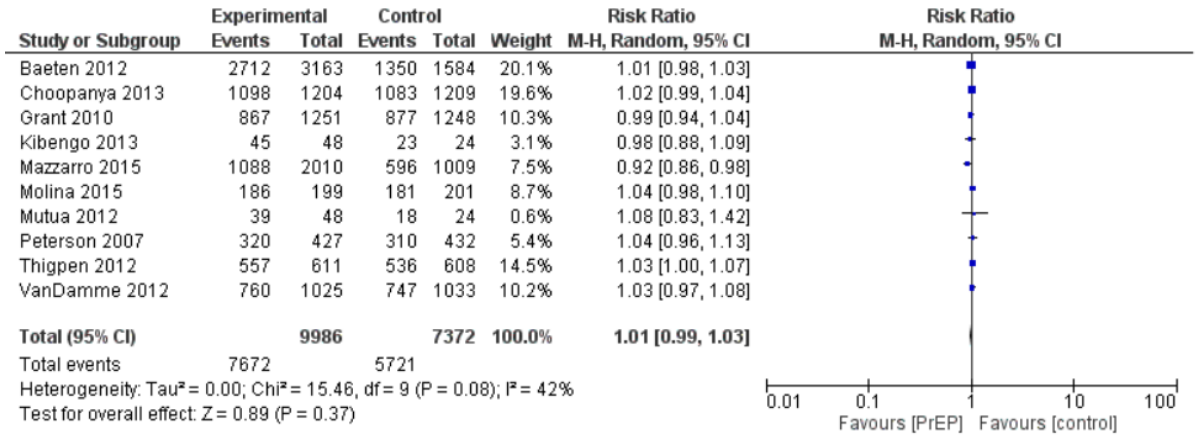


Figure S8. Meta-analysis: 'any adverse event', tenofovir/emtricitabine versus tenofovir

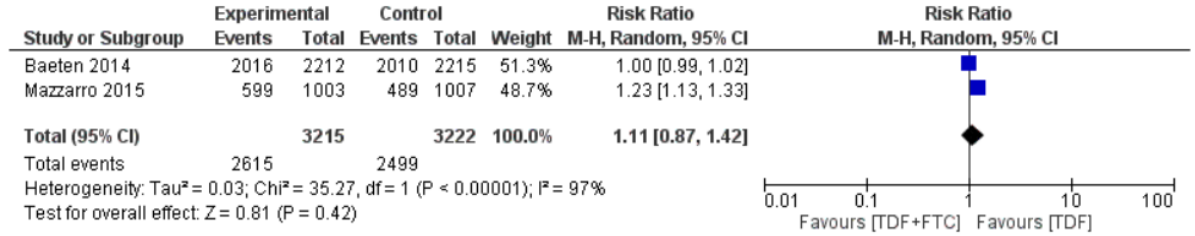
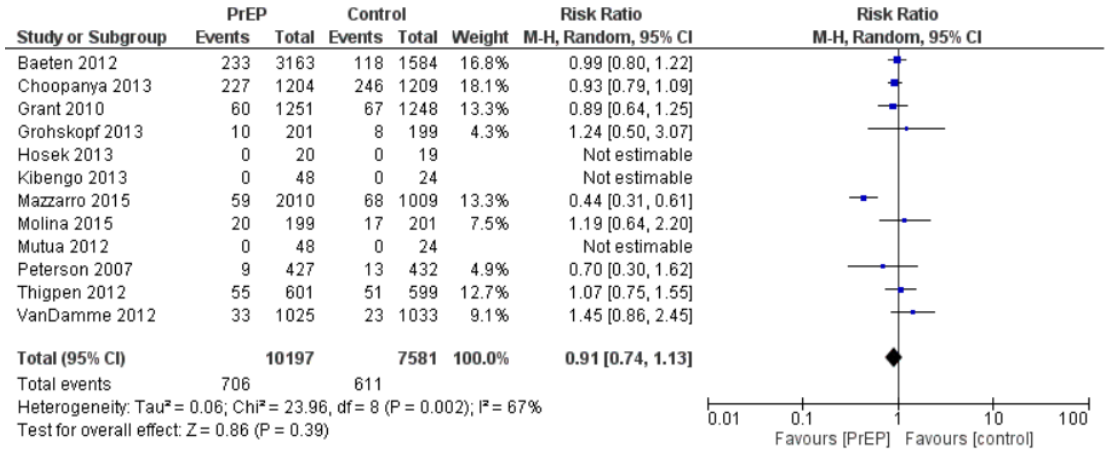
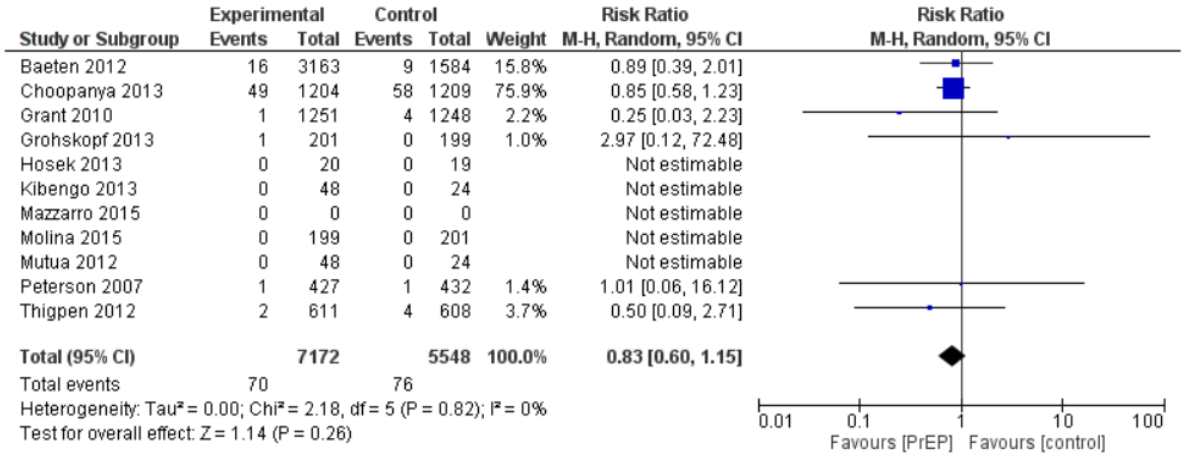


Figure S9. Meta-analysis: serious adverse events, PrEP versus placebo



Supplementary Material

Figure S10. Meta-analysis: deaths, PrEP versus placebo



Viral drug resistance mutations

Figure S11. Meta-analysis: any drug mutation (acute HIV at enrolment), PrEP versus placebo

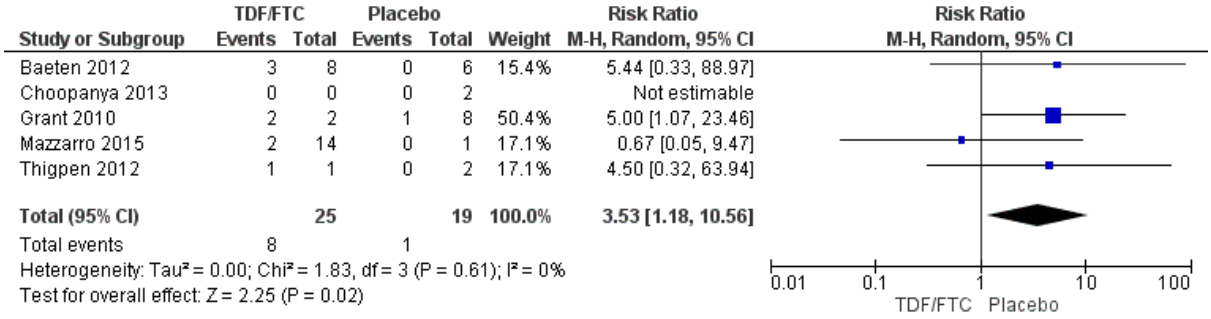
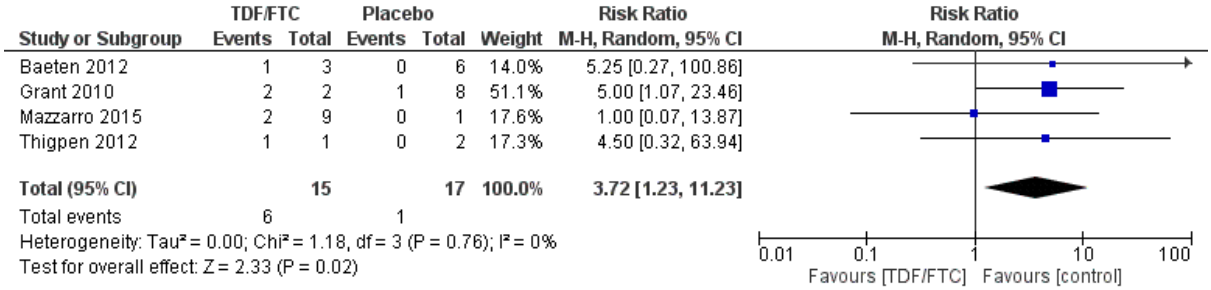


Figure S12. Meta-analysis: emtricitabine mutation (acute HIV at enrolment), tenofovir/emtricitabine versus placebo



S2.5

Results from Thigpen 2012 (by gender)

Number of HIV infections and PrEP efficacy by gender

	Tenofovir-emtricitabine group	Placebo group	Efficacy	95% CI	p-value
Female	7	14	49.4	-21.5, 80.8	0.11
Male	2	10	80.1	24.6, 96.9	0.03

Cohort is modified intention-to-treat; note that disaggregated data on overall number of male and female participants in each study arm not reported, precluding the evaluation of absolute risk.

S2.6 Adherence, as measured in primary studies

Study	Intervention	Adherence
Bekker 2018 (ADAPT Cape Town)	Tenofovir/emtricitabine (daily, time and event-driven PrEP)	• 75% (7,283 of 9,652 doses taken) for daily regimen; 65% (2,367 of 3,616 doses taken) for time-driven regimen and 53% (1,161 of 2,203 doses taken) for those event-driven regimen by electronic drug monitoring.
Baeten 2012 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (three arms: two active arms and one placebo arm)	• Factoring in missed visits, other reasons for non-dispensation of study medication and non-adherence to dispensed study pills, 92.1% of follow-up time was covered by study medication. • Among 29 subjects on the tenofovir and emtricitabine/tenofovir arms who acquired HIV-1, 31% had tenofovir detected in a plasma sample at the seroconversion visit compared with 82% of 902 samples from a randomly-selected subset of 198 subjects who did not acquire HIV-1.
Baeten 2014 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (two active arms)	• Study medication was taken by participants on 90.0% of days during follow-up time (factoring in protocol-defined study medication interruptions, missed visits, and non-adherence to dispensed study pills, as measured by monthly pill counts of returned study tablets). • Among subjects who acquired HIV-1, the minority (14/51, 27.5%) had tenofovir detected in a plasma sample at the visit at which HIV-1 seroconversion was detected, compared with the majority (1,047/1,334, 78.5%) of samples from a randomly selected subset of subjects who did not acquire HIV-1.
Choopanya 2013 (Bangkok Tenofovir Study)	Tenofovir (daily)	• Adherence was assessed daily at directly observed therapy (DOT) visits and monthly at non-DOT visits using a study drug diary. On the basis of participants' study drug diaries, participants took the study drug an average (mean) of 83.8% of days. • Plasma samples were obtained from 46 participants with incident HIV infections the day infection was detected, and from 282 HIV-negative participants to test for the presence of tenofovir. Tenofovir was detected in one (1%) of 177 participants in the placebo group and 100 (66%) of 151 participants in the tenofovir group. • In the case-control analysis in participants assigned to tenofovir, tenofovir was detected in the plasma of 5 (39%) of 13 HIV-positive participants and 93 (67%) of 138 HIV-negative participants.
Grant 2010 (iPrEx)	Tenofovir/emtricitabine (daily)	• The rate of self-reported pill use was lower in the emtricitabine–tenofovir group than in the placebo group at week 4 (mean, 89% vs. 92%) and at week 8 (mean, 93% vs. 94%) but was similar thereafter (mean, 95% in the two groups). • The percentage of pill bottles returned was 66% by 30 days and 86% by 60 days. • Among subjects in the emtricitabine–tenofovir group, at least one of the study-drug components was detected in 3 of 34 subjects with HIV infection (9%) and in 22 of 43 seronegative control subjects (51%).

Grohskopf 2013 (CDC Safety Study)	Tenofovir (daily)	• Adherence was measured by pill count, medication event monitoring system (MEMS) and self-report; adherence ranged from 77% (pill count) to 92% (MEMS).
Kibengo 2013 (IAVI Uganda Study)	Tenofovir/emtricitabine (daily or intermittent)	• Median MEMS adherence rates were 98% (IQR: 93–100) for daily PrEP regimen, 91% (IQR: 73–97) for fixed intermittent dosing and 45% (IQR: 20–63) for post-coital dosing. • There was no difference in adherence rates between active and placebo groups, thus these two groups were combined for the adherence analyses.
Hosek 2013 (Project PrEPare)	Tenofovir/emtricitabine (daily)	• Self-reported medication adherence averaged 62% (range 43–83%) while rates of detectable tenofovir in plasma of participants in the emtricitabine/tenofovir arm ranged from 63.2% (week 4) to 20% (week 24).
Mazzarro 2015 (VOICE)	Tenofovir (oral), tenofovir/emtricitabine (oral) and vaginal tenofovir gel (all daily)	• 90% by self-report, 86% by returned products and 88% as assessed with audio computer-assisted self-interviewing (ACASI). • In a random sample, tenofovir was detected in 30%, 29% and 25% of available plasma samples from participants randomly assigned to receive tenofovir, tenofovir/emtricitabine and tenofovir gel, respectively.
McCormack 2015 (PROUD)	Tenofovir/emtricitabine (daily)	• Overall, sufficient study drug was prescribed for 88% of the total follow-up time. • Tenofovir was detected in plasma of all 52 sampled participants (range 38–549 ng/mL) who reported that they were taking PrEP.
Molina 2015 (Ipergay)*	Tenofovir/emtricitabine (intermittent)	• Median pills per month: 15 pills. • In the tenofovir–emtricitabine group, the rates of detection were 86% for tenofovir and 82% for emtricitabine, respectively, a finding that was consistent with receipt of each drug within the previous week. Tenofovir and emtricitabine were also detected in eight participants in the placebo group, three of whom were receiving postexposure prophylaxis. • Computer-assisted structured interviews also performed to assess most recent sexual episode. Overall, 28% of participants did not take tenofovir-emtricitabine or placebo, 29% took the assigned drug at a suboptimal dose and 43% took the assigned drug correctly.
Mutua 2012 (IAVI Kenya Study)	Tenofovir/emtricitabine (daily or intermittent)	• There was no difference in adherence rates between treatment and placebo groups, thus these groups were combined for the adherence analyses. Median MEMS adherence rates were 83% (IQR: 63–92) for daily dosing and 55% (IQR:28–78) for fixed intermittent dosing (p=0.003).
Peterson 2007 (West Africa Study)	Tenofovir (daily)	• The amount of product used was estimated by subtracting the number of pills returned from the number dispensed, and dividing this number by the total number of days in the effectiveness analysis. • Drug was used no more than 69% of study days. Excluding time off product due to pregnancy, drug was used for no more than 74% of study days.

Thigpen 2012 (TENOFOVIR2)	Tenofovir/emtricitabine (daily)	• The two groups had similar rates of adherence to the study medication as estimated by means of pill counts (84.1% in the tenofovir–emtricitabine group and 83.7% in the placebo group, P = 0.79) and self-reported adherence for the preceding 3 days (94.4% and 94.1%, respectively; P = 0.32). • Among the four participants in the tenofovir–emtricitabine group who became infected with HIV during the study, two (50%) had detectable levels of tenofovir and emtricitabine in plasma obtained at the visit before and closest to their estimated seroconversion dates. Among a small sample who did not undergo seroconversion, 55 (80%) and 56 (81%) had detectable levels of tenofovir and emtricitabine, respectively.
VanDamme 2012 (FEM-PrEP)	Tenofovir/emtricitabine (daily)	• At the time of study-drug discontinuation, 95% of participants reported that they had usually or always taken the assigned drug. Pill-count data were consistent with ingestion of the study drug on 88% of the days on which it was available to the participants. • In contrast, drug-level testing revealed much lower levels of adherence. Among women with seroconversion in the tenofovir–emtricitabine group, the target plasma level of tenofovir was identified in 7 of 27 women (26%) at the beginning of the infection window (excluding six women for whom the window started at enrolment), in 7 of 33 (21%) at the end of the window, and in 4 of 27 (15%) at both visits. Among the uninfected control participants, the numbers of women with target-level tenofovir were somewhat higher: 27 of 78 women (35%) at the beginning of the infection window, 35 of 95 (37%) at the end of the window, and 19 of 78 (24%) at both visits.

Tenofovir = Tenofovir Disoproxil Fumarate

* non-daily regimen

S2.7 Change in sexual behaviour/STI rates

Study	Measure	Outcome
Baeten 2012 (Partners PrEP)	• Having sex without a condom with HIV-positive partners in prior month • STI diagnoses from sex acts outside partnership	• At enrolment, 27% of HIV-1 seronegative partners reported sex without condoms with their HIV-1 seropositive partner during the prior month. This percentage decreased during follow-up (to 13% and 9% at 12 and 24 months) and was similar across the study arms. • The proportion reporting outside partnerships and who acquired sexually transmitted infections during follow up did not differ across the study arms.
Baeten 2014 (Partners PrEP)	Unreported	
Bekker 2018 (ADAPT Cape Town)	Unreported	
Choopanya 2013 (Bangkok Tenofovir Study)	• Drug use behaviour • Number of sexual partners	• Tenofovir and placebo recipients reported similar rates of injecting and sharing needles and similar numbers of sexual partners during follow up with no interactions between time and treatment group. • Overall, number of participants reporting injecting drugs or sharing needles reduced over time. • Sex with more than one partner decreased from 522 (22%) at enrolment to 43 (6%) at month 72.
Grant 2010 (iPrEx)	• Number of anal sex acts • Proportion of anal sex acts with a condom • STI diagnoses	• Sexual practices were similar in the two groups at all time points. • The total numbers of sexual partners with whom the respondent had receptive anal intercourse decreased, and the percentage of those partners who used a condom increased after subjects enrolled in the study. • There were no significant between-group differences in the numbers of subjects with syphilis, gonorrhea, chlamydia, genital warts or genital ulcers during follow-up.
Grohskopf 2013 (CDC Safety Study)	Unreported	
Hosek 2013 (Project PrEPare)	Male-to-male unprotected anal sex acts	• No significant differences among the three treatment groups across visits. • Insignificant trend from baseline to week 24 of decreasing unprotected anal sex acts across all treatment arms.
Kibengo 2013 (IAVI Uganda Study)	HIV behaviour change	• The median number of sexual partners in the past month remained at 1 (IQR: 1–1) during the trial. • No other HIV risk behaviours reported at baseline changed during the trial
Mazzarro 2015 (VOICE)	Unreported	
McCormack 2015 (PROUD)	• Number of sexual partners • Incident STIs	• Total number of different anal sex partners varied widely between baseline and year 1. No significant difference between groups at one year was detected. • Proportion with confirmed rectal chlamydia/gonorrhea was similar in immediate and delayed arms (proxy for condomless anal intercourse). • Adjusted odds ratio for rectal chlamydia or gonorrhea: 1.00 (0.72–1.38) (adjusted for number of sexual health screens)

Molina 2015 (Ipergay)	• Total number of sexual intercourse events • Proportion of events without a condom • Number of sexual partners • Incident STIs	• Sexual practices did not change overall among the participants during the study period as compared with baseline: there were no significant between group differences in the total number of episodes of sexual intercourse in the four weeks before, in the proportion of episodes of receptive anal intercourse without condoms, or in the proportion of episodes of anal sex without condoms during the most recent sexual intercourse. • There was a slight but significant decrease in the number of sexual partners within the past two months in the placebo group as compared with the tenofovir—emtricitabine group (7.5 and 8, respectively; p = 0.001). • The proportions of participants with a new sexually transmitted infection (of the throat, anus, and urinary tract combined) during follow-up were similar, with 41% in the tenofovir—emtricitabine group and 33% in the placebo group (P = 0.10).
Mutua 2012 (IAVI Kenya Study)	HIV behaviour change	• The median number of sexual partners in the past month increased from three (IQR 2–4) at baseline to four (IQR 2–8) at month 4 during the trial. • Because there may have been underreporting of sex partners at baseline, authors also compared the median number of sexual partners month 2 (4) and at month 4 (4).
Peterson 2007 (West Africa Study)	• Condom use at last sex • Number of sex acts • Number of partners	• During screening, participants reported an average of 12 coital acts per week with an average of 21 sexual partners in the previous 30 days (including 11 new partners). During follow-up, participants reported an average of 15 coital acts per week, with an average of 14 sexual partners in the previous 30 days (six new partners). Of note, most participants in this study were sex workers. • Self-reported condom use increased from 52% at screening (average across all sites during the last coital act prior to screening) to approximately 92% at the enrolment, month 3, month 6, and month 9 visits, to 95% at the month 12 visit (for acts occurring during the last seven days). The average condom use during the follow-up period was 92%.
Thigpen 2012 (TENOFOVIR2)	• Protected sex episodes with main/ most recent casual partner • Number of sexual partners	• The percentage of sexual episodes in which condoms were used with the main or most recent casual sexual partner was similar in the two study groups at enrolment (81.4% [range, 76.6 to 86.4] in the tenofovir–emtricitabine group and 79.2% [range, 71.6 to 87.6] in the placebo group, P = 0.66) and remained stable over time. • The reported number of sexual partners declined in both groups during the course of the study.
VanDamme 2012 (FEM-PrEP)	• Number of partners • Sex acts without a condom • Pelvic STIs	• There was no evidence of increased HIV risk behaviour during the trial, with modest but significant reductions in the numbers of partners (mean reduction, 0.14; P<0.001 by paired-data t-test), vaginal sex acts (mean reduction, 0.58; P<0.001), and sex acts without a condom (mean reduction, 0.46; P<0.001) reported by women at the last follow-up visit, as compared with seven days before enrolment.

		• Fewer than half the study participants agreed to undergo a pelvic examination. There were no significant between-group differences in the prevalence of pelvic STIs.

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

	Reporting Item	Page Number
Title		
#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract		

Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	6
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	7
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	8

Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	8
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material 2
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	7
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	8
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	Supplementary Material 2
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	8

Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	9
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	13
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Supplementary Material 2

Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	16-23 and Supplementary Material 2
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	16-23 and Supplementary Material 2
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	GRADE assessment and Supplementary Material 2
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	21
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	25
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	26

Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28

Funding

Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	1

Notes:

- 8: Supplementary Material 2
- 11: Supplementary Material 2
- 19: Supplementary Material 2
- 20: 16-23 and Supplementary Material 2
- 21: 16-23 and Supplementary Material 2
- 22: GRADE assessment and Supplementary Material 2 This checklist was completed on 20. December 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Oral Pre-exposure Prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048478.R2
Article Type:	Original research
Date Submitted by the Author:	04-Feb-2022
Complete List of Authors:	O Murchu, Eamon; Health Information and Quality Authority; Trinity College Marshall, Liam; Health Information and Quality Authority Teljeur, Conor; Health Information and Quality Authority Harrington, Patricia; Health Information and Quality Authority Hayes, Catherine; University of Dublin Trinity College, Public Health and Primary Care Moran, Patrick; Health Information and Quality Authority; Trinity College Ryan, Mairin; Health Information and Quality Authority; Trinity College, Department of Pharmacology & Therapeutics
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Infectious diseases, Health policy, Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, PUBLIC HEALTH, INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Oral Pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations

Authors: Eamon O Murchu, MB BCh BAO, MPH;[a, b] Liam Marshall, MSc;[a] Conor Teljeur, PhD;[a] Patricia Harrington, PhD;[a] Catherine Hayes, MD, MPH, MB;[b] Patrick Moran, PhD;[a, b] Máirín Ryan, PhD.[a, c]

[a]Health Information and Quality Authority, George's Court, George's Lane, Dublin 7, Ireland

[b]Trinity College Dublin, Institute of Population Health, Tallaght, Dublin 24, Ireland

[c]Trinity College Dublin, Department of Pharmacology & Therapeutics, Trinity Health Sciences, Dublin 8, Ireland

Corresponding author: Eamon O Murchu. Trinity College Dublin, Institute of Population Health, Tallaght, Dublin 24, Ireland. E-mail: eamonvalmont@gmail.com.

Word count: Abstract=300; Main text (excluding abstract, tables, figures, references): 4,698.

Figures=4; **Tables**=5; **Supplementary Material**=3 (S1 – protocol, S2 – search strategy, S3 – additional results); **PRISMA Checklist**=1

Abstract

Objective

To conduct a systematic review and meta-analysis of randomised controlled trials (RCTs) of the effectiveness and safety of oral Pre-Exposure Prophylaxis (PrEP) to prevent HIV.

Methods

Databases (PubMed, Embase, the Cochrane Register of Controlled Trials) were searched up to 5/7/2020. Search terms for 'HIV' were combined with terms for 'PrEP' or 'tenofovir/emtricitabine'. RCTs were included that compared oral tenofovir-containing PrEP to placebo, no treatment or alternative medication/dosing schedule. The primary outcome was the rate ratio (RR) of HIV infection using a modified intention-to-treat analysis. Secondary outcomes included safety, adherence and risk compensation. All analyses were stratified a priori by population: men who have sex with men (MSM), serodiscordant couples, heterosexuals and people who inject drugs (PWID).

The quality of individual studies was assessed using the Cochrane Risk-of-Bias tool and the certainty of evidence was assessed using GRADE.

Results

Of 2,803 unique records, 15 RCTs met our inclusion criteria. Over 25,000 participants were included, encompassing 38,289 person-years of follow-up data.

PrEP was found to be effective in MSM (Rate Ratio [RR] 0.25, 95% CI: 0.1-0.61; Absolute Rate Difference [RD] -0.03, 95% CI: -0.01 to -0.05), serodiscordant couples (RR 0.25, 95% CI:

0.14-0.46; RD -0.01, 95% CI: -0.01 to -0.02) and PWID (RR 0.51, 95% CI: 0.29-0.92; RD -0.00, 95% CI: -0.00 to -0.01), but not in heterosexuals (RR 0.77, 95% CI: 0.46-1.29).

Efficacy was strongly associated with adherence (p<0.01). PrEP was found to be safe, however unrecognised HIV at enrolment increased the risk of viral drug resistance mutations. Evidence for behaviour change or an increase in STIs was not found.

Conclusions

PrEP is safe and effective in MSM, serodiscordant couples and PWID. Additional research is needed prior to recommending PrEP in heterosexuals. No RCTs reported effectiveness or safety data for other high-risk groups, such as transgender women and sex workers.

PROSPERO ID: CRD42017065937

Keywords: ‘PrEP’, ‘pre-exposure prophylaxis’, ‘HIV’, ‘meta-analysis’

Article Summary

Strengths and limitations of this study

- A systematic review and meta-analysis of RCTs was conducted of the efficacy and safety of oral PrEP to prevent HIV following best practice guidelines (PRISMA guidelines and GRADE framework)
- Observational studies were excluded from this review, and as such, PrEP effectiveness may be lower in real-world settings
- Change in sexual behaviour, or 'risk compensation', is difficult to ascertain based on RCT evidence alone
- Due to substantial variation in adherence across studies, findings should be interpreted with caution.

Introduction

While the incidence of HIV has declined worldwide over the past decade, 1.5 million new HIV infections occurred in 2020,[1] highlighting the ongoing need for new and effective HIV prevention initiatives. Pre-exposure prophylaxis (PrEP) is a novel biomedical form of HIV prevention method, whereby oral anti-retrovirals (most commonly a combination of tenofovir and emtricitabine) are taken by individuals at high risk of HIV acquisition to prevent infection. PrEP aims to complement the existing arsenal of HIV prevention strategies, such as the promotion of safer sex practices, treatment-as-prevention and post-exposure prophylaxis after sexual exposure.

In 2014, the WHO recommended offering PrEP to men who have sex with men (MSM),[2] based a 2010 trial that demonstrated the effectiveness in this group.[3] Subsequently, in 2015, they broadened the recommendation to include anyone at substantial risk of HIV infection (defined as risk of 3 per 100 person-years in the absence of PrEP),[4] based on further evidence of the acceptability and effectiveness in other populations. While the success of early PrEP studies in MSM was replicated in the years that followed (with high efficacy noted in IPERGAY[5] and PROUD[6] clinical trials), uncertainty still exists in other key populations. Many initial studies that failed to demonstrate effectiveness were plagued by poor adherence, such as those that enrolled heterosexual women.[7] Also, of major concern to public health officials and policy-makers is the potential occurrence of 'risk compensation' in PrEP users (an increase in unsafe sexual practices due to the knowledge that PrEP is protective against HIV), which may lead to an increase in STIs, exacerbating the secular trend of rising STI rates in many countries.

Since the most recent WHO recommendation, a number of new trials in diverse populations have been conducted. We therefore conducted a systematic review and meta-analysis to retrieve the most up-to-date evidence on the effectiveness and safety of oral PrEP compared with placebo, no treatment or alternative oral PrEP medication/dosing schedule in all populations, with a particular emphasis on adherence and risk compensation. This review aimed to inform the decision of the Irish government to implement a PrEP programme and to assist in the development of national clinical practice guidelines on PrEP for HIV prevention.

Methods

A systematic review and meta-analysis of randomised controlled trials (RCTs) was conducted, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[9] This framework is commonly used internationally to aid decisions by policy-makers, and ensured a systematic and transparent approach in the development of clinical practice recommendations. This study was registered with PROSPERO (ID: CRD42017065937) and followed an agreed protocol (Supplementary Material 1).

Search strategy and selection criteria

Electronic searches were conducted in Medline (PubMed), Embase, the Cochrane Register of Controlled Trials, CRD DARE Database, Morbidity and Mortality Weekly Report (CDC), and Eurosurveillance reports. Search terms that related to 'HIV' were combined with search terms that related to 'PrEP' or 'tenofovir', and filters for study design (RCTs) were applied (the full search strategy for PubMed is provided in Supplementary Material 2). Databases were searched on 5 July 2020. No restrictions were placed based on location of the intervention or date of publication. No language restrictions were used; articles in languages other than English were translated where necessary. Table 1 outlines the inclusion criteria for study selection. Animal studies, studies that did not report primary outcome data (HIV incidence), and abstracts from conference proceedings were excluded.

It was decided a priori that all analyses of effectiveness would be stratified by population. The four populations were men who have sex with men (MSM), serodiscordant

heterosexual couples (individuals whose partners are HIV positive and not virally suppressed on antiretroviral medications), heterosexuals and people who inject drugs (PWIDs).

Table 1. Inclusion criteria for studies

Population	Populations at substantial risk of HIV, including men who have sex with men, serodiscordant heterosexual couples, heterosexuals and people who inject drugs
Intervention	Oral tenofovir-containing pre-exposure prophylaxis
Comparator	Placebo, no treatment or alternative oral PrEP medication/dosing schedule
Outcomes	Primary outcome: Relative risk of HIV infection Secondary outcomes: 1. Adherence to PrEP 2. Adverse events 3. Incidence of other STIs and behaviour change associated with PrEP use 4. Viral drug mutations among those who contract HIV
Studies	RCTs

Legend: PrEP – pre-exposure prophylaxis, RCT – randomised controlled trial, STI – sexually transmitted infection.

Data collection

Results of the database search were exported to Endnote X7. Full text articles were obtained for all citations identified as potentially eligible. Two reviewers (EOM and LM) independently screened these according to the pre-specified inclusion criteria. Two reviewers (EOM and LM) independently performed data extraction and assessed the risk of bias according to the Cochrane Risk of Bias tool.[10] An overall assessment of the quality of the evidence was assessed using the GRADE approach that included an assessment of other biases, such as publication bias.[9]

Statistical analysis

The primary outcome measure was the rate ratio (RR) of HIV infection for each population. The rate of HIV infection represented the number of HIV infections that occurred per person-years of follow up data, and the RR compares the rate of HIV infection in the PrEP

group with control. The rate of HIV infection (per person-years) was favoured over risk of HIV infection as rate incorporates both the number of participants *and* the duration of follow-up, allowing for comparisons across studies that may vary significantly in terms of study duration. The absolute rate difference (RD) of HIV infection was also estimated for each population; in this case, the RD represented the actual difference in the observed rate of HIV between PrEP and control groups per person-year of follow-up data. Meta-analyses of RRs and RDs were performed in Review Manager 5.3 using Mantel-Haenszel random effects models.

A modified intention-to-treat analysis was employed (and not per-protocol analysis); therefore, effectiveness was a function of both efficacy of the drug itself and on adherence. A modified intention-to-treat analysis was selected instead of a standard intention-to-treat analysis to account for unrecognised HIV infection at enrolment. In the modified intention-to-treat analysis, all patients who were HIV negative at enrolment in the study were included in analyses, and individuals with an unrecognised HIV infection prior to enrolment were excluded.

Clinical heterogeneity was assessed by the reviewers based on the description of the interventions and comparators in the RCTs. Statistical heterogeneity was examined using the I^2 statistic (I^2 values above 75% represented considerable heterogeneity, per Cochrane Handbook, Version 6.2, 2021, Chapter 10, section 10.10.2). If there was sufficient clinical homogeneity across studies, results were pooled using a random effects Mantel–Haenszel model.

In the estimation of PrEP effectiveness, subgroups of studies were defined by dosing schedule, comparator and adherence. Analyses were stratified by population and

adherence. Adherence was dichotomised for subgroup analyses: if the proportion of participants who were adherent was ≥80%, the study was considered 'high adherence' and <80% was considered 'low adherence'. Commonly used measures of adherence include self-report, pill counts, medication event monitoring systems (MEMS), structured interviews and plasma drug detection methods. Plasma drug monitoring is considered the gold standard for adherence assessment; plasma drug detection was favoured over self-report/pill count in the determination of adherence as it minimises recall bias. In studies that only measured plasma drug concentration in participants who reported taking study drug, the proportion of samples with study drug detected was multiplied by the self-reported adherence rate. In studies that measured adherence in a number of ways without undertaking plasma drug monitoring, taking a conservative approach, the lowest estimate of adherence was used for subgroup analysis.

To investigate the relationship between efficacy and adherence, a meta-regression analysis was conducted (meta-regression was considered the appropriate model as it accounts for trial size in analyses). In this analysis, adherence was a continuous variable, and only studies that confirmed adherence through plasma drug monitoring were included. Analyses were conducted in R version 3.6.2, including the meta R package.

In the assessment of the safety of PrEP, the definitions for adverse events and serious adverse events followed the definitions used in the primary studies. Outcome measures were expressed as both RRs of safety events and RDs between groups. In the assessment of behaviour change, the effect of PrEP on condom use, number of sexual partners, recreational drug use and the rate of new STI diagnoses (as a proxy for condomless sex) were assessed. In the assessment of PrEP-related drug mutations, subgroups included

patients with unrecognised acute HIV infection at the time of enrolment and patients who seroconverted during the course of the trial. Where there was a lack of data or agreed definitions for these outcomes, a narrative review was performed.

In the case of pooling data for rare events, there can be issues with the inclusion of studies with zero events in one or both arms.[11] A common approach where there are zero events in one arm is to apply a continuity correction, whereby all cells in the two by two table for a given study have 0.5 added to avoid division by zero. This approach can lead to bias, particularly for small trials or those with imbalanced arms. Trials with zero events in both arms are typically excluded, leading to a loss of information. Approaches are available to include zero event trials with application of a continuity correction. For this study, if trials with zero events in one or both arms were identified, a sensitivity analysis using a random effects Poisson regression[11] and beta-binomial[12] models was applied to determine whether the results were sensitive to presence of trials with zero events in one or both arms. The main analysis excluded trials with zero events in both arms, as has been recommended when a treatment effect is considered likely.[13]

In the assessment of publication bias, funnel plots were used when there were more than 10 studies available for analysis. Standard approaches to funnel plots and tests for small study bias use the log(OR) or log(RR), which are not independent of their estimated standard error creating a bias. Those tests also have the limitation that they omit studies that have zero events in both arms. To overcome these issues, the arcsine test for publication bias was used.[14]

Patient and public involvement

Patients or the public were not involved in this research.

Ethics approval statement

This study did not require ethics approval as no human participants were involved.

Results

A total of 2,803 unique records were retrieved, resulting in 73 studies for full text review (Figure 1 provides the PRISMA diagram of study selection and the list of excluded studies, along with reasons, is provided in Supplementary Material 3.1). Fifteen RCTs met our inclusion criteria and were included in the assessment of effectiveness and safety. Seven RCTs were placebo-controlled trials that evaluated daily oral PrEP.[3 7 15-19] Two studies randomised participants to receive either immediate or delayed PrEP.[6 20] Three placebo-controlled trials investigated non-daily PrEP, including intermittent and 'on-demand' (also known as event-based) PrEP.[5 21 22] Two RCTs did not contain a 'no PrEP' arm (placebo or no medication): one compared tenofovir with tenofovir/emtricitabine[23] and one compared three different PrEP dosing schedules.[24] One study contained three arms: PrEP, placebo and 'no pill'.[25] Four distinct patient populations were assessed. Six RCTs enrolled MSM,[3 5 6 20 21 25] five enrolled heterosexual participants,[7 16 17 19 24] three enrolled serodiscordant couples[18 22 23] and one enrolled PWIDs.[15]

Figure 1. PRISMA diagram of study selection

Figure 1 Legend: Diagram provides details on the selection process of studies for inclusion. Note that the exclusion of 2,703 citations at the 'screening' stage did not meet our study inclusion/exclusion criteria based on screening of title/abstract.

Included studies involved 25,051 participants encompassing 38,289 person-years of follow-

up data. Of the 15,062 participants that received active drug in the intervention arms of trials, 55% received combination tenofovir/emtricitabine and 45% received single agent tenofovir. Follow-up periods ranged from 17 weeks to 6.9 years. Four trials were conducted in high-income countries (USA, England, France and Canada), 10 in low- or middle-income countries (including nine trials in sub-Saharan Africa) and one was a multicenter trial conducted across four continents. All studies reported the results of a modified intention-to-treat analysis.

The main characteristics of included studies are provided in Table 2.

Table 2. Study characteristics

Study	Location	Population	Intervention	Comparison	No. participants	Follow-up (PYs)	Adherence: high (≥80%) vs. low (<80%)*
MSM							
Hosek 2013 (Project PrEPare)[25]	USA	MSM. Median age: 20 years	TDF/FTC	Daily PrEP vs placebo or 'no pill'	58	27	Low: 62% by self-report
Grohskopf 2013 (CDC Safety Study)[20]	USA	MSM. Age range: 18–60 years	TDF	Immediate or delayed PrEP vs immediate or delayed placebo	400	800	Low: 77% by pill count
iPrEx (Grant 2010)[3]	Brazil, Ecuador, South Africa, Peru, Thailand, USA	MSM (99%) and transgender women (1%). Age range: 18–67 years.	TDF/FTC	Daily PrEP vs placebo	2499	3324	Low: 51% by plasma drug detection
McCormack 2015 (PROUD)[6]	UK	MSM. Median age: 35 years	TDF/FTC	Immediate PrEP vs delayed PrEP	544	504	High: 88% (self-report and plasma drug detection**)
Molina 2015 (IPERGAY)[5]	Canada, France	MSM. Median age 34.5 years	TDF/FTC	Intermittent ('on demand') PrEP vs placebo***	400	431	High: 86% by plasma drug detection
Mutua 2012 (IAVI Kenya Study)[21]	Kenya	MSM (93%) and female sex workers (7%). Mean age: 26 years	TDF/FTC	Daily or intermittent PrEP vs daily or intermittent placebo	72	24	High: 83% by MEMS
Serodiscordant heterosexual couples (when the HIV-positive partner is not on antiretroviral treatment)							
Kibengo 2013 (IAVI Uganda Study)[22]	Uganda	Serodiscordant couples (negative partner: 50% male). Mean age: 33 years	TDF/FTC	Daily or intermittent PrEP vs daily or intermittent placebo	72 couples	24	High: 98% by MEMS
Baeten 2012 (Partners PrEP Study)[18]	Kenya, Uganda	Serodiscordant couples (negative partner: 61–64% male). Age range: 18–45 years	TDF/FTC and TDF only	Daily PrEP vs placebo	4,747 couples	7,830	High: 82% by plasma drug detection

Study	Location	Population	Intervention	Comparison	No. participants	Follow-up (PYs)	Adherence: high (≥80%) vs. low (<80%)*
Baeten 2014 (Partners PrEP Study Continuation)[23]	Kenya and Uganda	Serodiscordant couples (negative partner: 62–64% male). Age range: 28–40 years	TDF/FTC and TDF only	TDF/FTC vs TDF	4,410 couples	8,791	Low: 78.5% by plasma drug detection
Heterosexuals							
Bekker 2018 (ADAPT Cape Town)[24]	South Africa	Women. Median age: 26 years	TDF/FTC	Daily, time and event-driven PrEP	191	99	Low: 53-75% by MEMS
Marrazzo 2015 (VOICE)[19]	South Africa, Uganda, Zimbabwe	Women. Median age: 24 years	5 arms: TDF/FTC, TDF only, 1% TDF vaginal gel, oral placebo and placebo vaginal gel	Daily PrEP vs placebo	4,969	5,509	Low: 29% by plasma drug detection
Peterson 2007 (West African Safety Study)	Nigeria, Cameroon, Ghana	Women. Age range: 18–34 years	TDF	Daily PrEP vs placebo	936	428	Low: 69% by pill count
Thigpen 2012 (TENOFOVIR2)[16]	Botswana	Heterosexual men (54.2%) and women (45.8%). Age range: 18–39 years	TDF/FTC	Daily PrEP vs placebo	1219	1,563	High: 84.1% by pill count
VanDamme 2012 (FEM-PrEP)[7]	Tanzania, South Africa, Kenya	Women. Median age: 24.2 years	TDF/FTC	Daily PrEP vs placebo	2,120	1407	Low: 24% by plasma drug detection
PWIDs							
Choopanya 2013 (Bangkok Tenofovir Study)[15]	Thailand	PWID (80% male). Median age: 31 years	TDF	Daily PrEP vs placebo	2,413	9,665	Low: 67% by plasma drug detection

Table 2 Legend: FTC = emtricitabine. MSM = men who have sex with men; PWID = people who inject drugs. TDF = Tenofovir Disoproxil Fumarate. TDF/FTC = Tenofovir Disoproxil Fumarate and Emtricitabine fixed dose combination. MEMS = Medication Event Monitoring System. PY = person-years. UK = United Kingdom. USA = United States of America. In all cases, tenofovir dose was 300mg and emtricitabine dose was 200mg.

*Adherence refers to the proportion of participants in trials that adhered to study drug. In most studies, more than one method was used to measure adherence; taking a conservative approach, the lowest estimate of adherence was used. In trials that investigated daily and intermittent PrEP, adherence relates to daily PrEP. In studies that measured tenofovir and emtricitabine separately, adherence refers to tenofovir detection.

**PROUD trial: adherence was determined by a combination of self-report and plasma drug detection. Sufficient study drug was prescribed for 88% of the total follow-up time, and study drug was detected in 100% of participants who reported taking PrEP.

***'On demand' dosing: participants were instructed to take 2 pills of TDF/FTC or placebo 2 to 24 hours before sex, followed by a third pill 24 hours later and a fourth pill 48 hours later.

All included individual RCTs were judged to have a low risk of bias by the Cochrane Risk of Bias Tool (risk of bias graph and summary provided in Supplementary Material 3.2, Figures S1 and S2, respectively). Across studies, while publication bias may have been present in earlier, industry-funded studies (with fewer participants), this form of bias was considered less likely in the more recent, larger, publicly-funded studies. To investigate publication bias, the arcsine test for funnel plot asymmetry was applied to all 13 trials (as there were too few trials in individual population groups). The p-values for the equivalent of the Begg, Egger and Thompson tests were 0.58, 0.14 and 0.13, respectively. As such, it was determined that there was no evidence of funnel plot asymmetry (Figure 2).

Figure 2. Funnel plot for publication bias

Figure 2 Legend: The funnel plot of all studies (n=13) is presented. There is no evidence of significant small study bias.

Effectiveness

The following sections present the effectiveness of PrEP to prevent HIV acquisition by study population and stratified by adherence, where appropriate. Tables 3 and 4 present the GRADE 'summary of findings' assessment of the effectiveness and safety of PrEP (and a forest plot of all studies is provided in Supplementary Material 3.3, Figure S3).

Table 3. GRADE summary of findings: PrEP effectiveness

Summary of findings table: Effectiveness of PrEP

Patient or population: HIV prevention in participants at substantial risk
Intervention: PrEP
Comparison: no PrEP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect, expressed as rate ratios (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Rate with no PrEP	Rate with PrEP				
HIV infection: **MSM** (all clinical trials)	40 per 1,000	**10 per 1,000** (4 to 24)	**RR 0.25** (0.10 to 0.61)	5,103 (6 RCTs)	⊕⊕⊕⊕ HIGH [a, b]	PrEP is effective in preventing HIV acquisition in MSM with a rate reduction of 75%
HIV infection: **MSM**, trials with high (≥80%) adherence	66 per 1,000	**9 per 1,000** (4 to 23)	**RR 0.14** (0.06 to 0.35)	960 (3 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is highly effective in preventing HIV acquisition in MSM in trials with high adherence (over 80%) with a rate reduction of 86%
HIV infection: **MSM**, trials with low (<80%) adherence**	32 per 1,000	**18 per 1,000** (12 to 26)	**RR 0.55** (0.37 to 0.81)	4143 (3 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing HIV acquisition in MSM in trials with low adherence (under 80%) with a rate reduction of 45%
HIV infection: **Serodiscordant couples***** (all clinical trials: two studies with high [≥80%] adherence)	20 per 1,000	**5 per 1,000** (3 to 9)	**RR 0.25** (0.14 to 0.46)	5,237 (2 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing HIV acquisition in serodiscordant couples with a rate reduction of 75%
HIV infection: **Heterosexual transmission** (all clinical trials)	41 per 1,000	**32 per 1,000** (19 to 53)	**RR 0.77** (0.46 to 1.29)	6,821 (4 RCTs)	⊕⊕◯◯ LOW[a, c]	PrEP is not effective in preventing heterosexual HIV transmission (all trials)
HIV infection: **Heterosexual transmission**, trials with high (≥80%) adherence	31 per 1,000	**12 per 1,000** (6 to 26)	**RR 0.39** (0.18 to 0.83)	1524 (1 RCT)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing heterosexual HIV transmission in heterosexuals in one trial with high (over 80%) adherence. This trial enrolled males and females; note that efficacy was only reported for males.

HIV infection: **Heterosexual transmission**, trials with low (<80%) adherence	45 per 1,000	**46 per 1,000** (34 to 64)	**RR 1.03** (0.75 to 1.43)	5297 (3 RCTs)	⊕⊕⊕◯ MODERATE[c]	PrEP is not effective in preventing heterosexual HIV transmission in trials with low adherence. Note that all three trials enrolled heterosexual women.
HIV infection: **People who inject drugs** (all clinical trials: one study with low [<80%] adherence)	7 per 1,000	**3 per 1,000** (2 to 6)	**RR 0.51** (0.29 to 0.92)	9,666 (1 RCT)	⊕⊕⊕◯ MODERATE[d]	PrEP is effective in preventing HIV transmission in people who inject drugs with a rate reduction of 49%

Table 3 Legend:
Explanations
a. Downgraded one level for heterogeneity b. Upgraded one level for large effect (RR<0.5) c. Downgraded one level for imprecision d. Downgraded one level for indirectness
***The rate in the intervention group** (and its 95% confidence interval) is based on the assumed rate in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Note that under alternative methods to account for zero events in one or both arms (beta-binomial), there is greater imprecision and the upper confidence bound crosses the line of no effect
***In studies that enrolled serodiscordant couples, the HIV-positive individual was not on antiretroviral therapy. All studies relate to serodiscordant heterosexual couples.
CI: Confidence interval; **RR:** Rate ratio
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 4. GRADE summary of findings: Safety of PrEP

Summary of findings table: Safety of PrEP

Patient or population: HIV prevention in participants at substantial risk. **Intervention**: PrEP. **Comparison**: no PrEP.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Rate with no PrEP	Rate with PrEP				
Safety outcome: Any adverse event	776 per 1,000	**784 per 1,000** (768 to 799)	**RR 1.01** (0.99 to 1.03)	17,358 (10 RCTs)	⊕⊕⊕⊕ HIGH	Adverse events do not occur more commonly in patients taking PrEP compared with placebo. Adverse events were common in trials (78% of patients reporting 'any' event).
Safety outcome: Serious adverse events	81 per 1,000	**73 per 1,000** (60 to 91)	**RR 0.91** (0.74 to 1.13)	17,778 (12 RCTs)	⊕⊕⊕⊕ HIGH	Serious adverse events do not occur more commonly in patients taking PrEP compared with placebo. Serious adverse events occurred in 7% of patients in trials but most were not drug related.
Safety outcome: Deaths	13 per 1,000	**10 per 1,000** (8 to 15)	**RR 0.83** (0.60 to 1.15)	12,720 (11 RCTs)	⊕⊕⊕◯ MODERATE[a]	Deaths did not occur more commonly in people taking PrEP compared with placebo in trials. No deaths were related to PrEP.
Safety outcome: Drug resistance mutations in patients with acute HIV at enrolment	53 per 1,000	**186 per 1,000** (62 to 556)	**RR 3.53** (1.18 to 10.56)	44 (5 RCTs)	⊕⊕⊕◯ MODERATE[a]	Patients randomised to receive PrEP who had acute HIV at enrolment were at increased risk of developing resistance mutations to the study drug. Most conferred resistance to emtricitabine.

Table 4 Legend:
Explanations
a. Imprecision was detected due to few observations.
Note that only a minority of studies tested for viral drug resistance mutations
*The rate in the intervention group (and its 95% confidence interval) is based on the assumed rate in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Rate ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Effectiveness in MSM

Six studies enrolled MSM.[3 5 6 20 21 25] A meta-analysis of all studies resulted in a RR of 0.25 (95% CI: 0.1 to 0.61), indicating a 75% reduction in the rate of HIV acquisition (Figure 3). The estimated absolute rate difference (RD) was -0.03 (95% CI: -0.01 to -0.05), indicating PrEP users had a 3% lower rate of HIV acquisition per person-year of follow-up.

When stratified by adherence (≥80% versus <80%), heterogeneity was eliminated (I^2 reduced from 52% to 0%). PrEP was most effective in studies with high adherence (≥80%), as expected, where rate of HIV acquisition was reduced by 86% (RR 0.14, 95% CI: 0.06 to 0.35; RD -0.06, 95% CI: -0.04 to -0.09; I^2 = 0%, n=3 studies).[5 6 21] Of the three studies with high adherence, one study was small and reported non-significant findings due to few events (Mutua et al.[21]). Of the remaining two studies, one study investigated daily PrEP use (McCormack et al., PROUD trial[6]) and the other investigated 'on demand' PrEP (Molina et al., IPERGAY trial[5]). Both studies reported identical efficacy (PROUD: RR 0.14, 95% CI 0.04-0.47; IPERGAY: RR 0.14, 95% CI 0.03-0.6).

When adherence was under 80%, acquisition rate was reduced by 45% (RR 0.55, 95% CI: 0.37 to 0.81; RD -0.01, 95% CI: -0.00 to -0.02; I^2 = 0%, n=3 studies).[3 20 23 25]

Figure 3. Meta-analysis: HIV acquisition in MSM, all studies

Figure 2 Legend: Forest plot of the meta-analysis of HIV incidence in all MSM trials, PrEP versus placebo or no drug. Subgroups include high (≥80%) adherence and low (<80%) adherence. 'Events' refers to new HIV infections and 'Total' refers to total person-years at risk during the study period.

Effectiveness in serodiscordant heterosexual couples

In all three studies that enrolled serodiscordant heterosexual couples, the HIV-infected partner was not on antiretroviral therapy (studies were conducted in Kenya and Uganda; HIV-infected participants did not meet criteria for ART initiation at the time of enrolment).[18 22 23] Details on the CD4 count (a type of cell that HIV infects) or viral load of the HIV-infected partners were not reported.

Two studies investigated the effect of daily oral PrEP compared to placebo.[18 22] A total of 4,819 couples were enrolled, and the seronegative individual was male in the majority (>60%) of cases. One trial enrolled few participants (n=24 in the daily PrEP arm), and the duration of the trial was very short (4 months); this study did not contribute to analyses as no seroconversions were reported in either arm of the trial.[22] The trial by Baeten et al.[18] consisted of three arms: tenofovir/emtricitabine (n=1,568 participants), tenofovir alone (n=1,572 participants) and placebo (n=1,568 participants). Tenofovir/emtricitabine resulted in a 75% rate reduction (RR 0.25, 95% CI: 0.14 to 0.46; RD -0.01, 95% CI: -0.01 to -0.02) and tenofovir alone resulted in a 67% rate reduction (RR 0.33, 95% CI: 0.19 to 0.56; RD -0.01, 95% CI: -0.01 to -0.02). A continuation of this trial (Baeten et al. 2014[23]) compared tenofovir/emtricitabine with tenofovir alone: there was no significant difference between groups.

Effectiveness in heterosexuals

Of the five studies enrolling heterosexual participants, four were placebo-controlled[7 16 17 19] and one compared different drug schedules.[24] Four studies enrolled only women[7 17 19 24] and one study enrolled both men and women.[16] All studies were conducted in a high HIV prevalence context (countries in Sub-Saharan Africa). A meta-analysis of the four placebo-controlled studies[7 16 17 19] did not demonstrate a statistically significant reduction in HIV

acquisition (RR 0.77, 95% CI: 0.46 to 1.29; I^2 = 66%, Figure S4, Supplementary Material 3.3). In the only trial with high adherence (Thigpen et al.[16]), a rate reduction of 61% was noted (RR 0.39, 95% CI 0.18 to 0.83; RD -0.02, 95% CI: -0.01 to -0.04). This was the only trial to enrol both men and women, and when the results were analysed separately by sex, efficacy was only noted in males, with a rate reduction of 80% (RR 0.2, 95% CI 0.04 to 0.91, Supplementary Material 3.4). As expected, in a meta-analysis of trials with low adherence, the result was non-significant (RR 1.03, 95% CI 0.75 to 1.43, I^2 = 21%, Figure S5, Supplementary Material 3.3).

A final study compared different PrEP regimens (daily PrEP, 'time-driven' PrEP and 'event-driven' PrEP).[24] Fewer infections occurred in the daily PrEP arm; however, there were no significant differences in HIV acquisition comparing either event or time-driven PrEP with daily PrEP.

Effectiveness in PWID

Only one study enrolled PWID.[15] Daily oral tenofovir was found to be effective, with a 49% reduction in HIV acquisition (RR 0.51, 95% CI: 0.29 to 0.92; RD -0.00, 95% CI: -0.00 to -0.01). In this study, HIV transmission may have occurred sexually or parenterally.

Sensitivity analysis

A sensitivity analysis was applied to determine whether the use of continuity correction and the omission of studies with zero events in both arms impacted on the results. First, a meta-analysis of all trials was conducted. Both the Poisson regression and beta-binomial models produced similar results to the standard approach (Table 5), providing reassurance that the impact of excluding smaller studies with zero events was small. Second, a meta-analysis of

studies in the MSM group was undertaken, stratified by adherence, as these analyses included three studies with zero events in one or both arms (Table 5). Only the beta-binomial model converged on a stable result. The rate ratio and 95% confidence interval were very similar to the main analysis for the high adherence group. However, there was greater imprecision in the low adherence group, and the wider confidence bounds included the possibility of no effect.

Table 5 Sensitivity analysis

Group	Method of analysis	Rate ratio	95% CI
All studies (n=13)	Standard approach (Mantel-Haenszel)	0.41	0.26 to 0.67
	Poisson regression	0.375	0.225 to 0.625
	Beta-binomial	0.437	0.210 to 0.911
MSM group: high adherence (n=3 studies)	Standard approach (Mantel-Haenszel)	0.14	0.06 to 0.35
	Beta-binomial	0.134	0.063 to 0.284
MSM group: low adherence (n=3 studies)	Standard approach (Mantel-Haenszel)	0.55	0.37 to 0.81
	Beta-binomial	0.428	0.038 to 4.815

Relationship between efficacy and adherence

A meta-regression analysis was performed to investigate the relationship between efficacy and adherence, accounting for trial size (Figure 4; simple regression line provided in Supplementary Material S3.3, Figure S6.). Adherence was measured in a variety of methods across trials (Supplementary Material 3.5). Studies that did not confirm adherence through plasma drug detection rates were excluded from meta-regression analyses, due to biases associated with other methods such as self-report or pill count.

Efficacy (as RRs) and adherence (by proportion with plasma drug detectable) were strongly associated ($p<0.001$). As the proportion adherent increases from 0.5 to 0.6, the RR

decreases by 0.13. Therefore, on average, a 10% decrease in adherence decreases efficacy by 13%.

Figure 4. Fitted meta-regression line of the relationship between trial-level PrEP adherence and efficacy

Figure 3 Legend: Only trials that reported plasma drug concentration from a representative sample contributed to analysis, represented as circles (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), VanDamme 2012 (FEM-PrEP). The solid line represents the fitted regression line and the shaded area the 95% Confidence Interval. The X-axis represents the trial-level adherence as a proportion and the Y-axis represents the efficacy as rate ratios.

Safety

Eleven studies reported data on 'any' adverse events, including ten that compared PrEP with placebo[3 5 7 15-19 21 22] and two that compared tenofovir alone to tenofovir/emtricitabine.[19 23] A meta-analysis of placebo-controlled trials demonstrated no significant difference between groups (RR 1.01; 95% CI 0.99 to 1.03; I^2 = 42%, Figure S7, Supplementary Material 3.3). Comparing tenofovir with tenofovir/emtricitabine, one study noted a small increase in adverse events in the tenofovir/emtricitabine group (RR 1.23; 95% CI 1.03 to 1.33, Figure S8, Supplementary Material 3.3)[19] and another failed to show any difference.[23]

Of note, several studies reported mild decreases in renal function among PrEP users that returned to normal following discontinuation of PrEP use, while a reduction in creatinine clearance (a measure of renal function) was not observed in others.[15 18] Where renal function has been affected, PrEP was associated with mild, non-progressive and reversible

reductions in creatinine clearance.[3 5 6 15 18] Some trials also found slight decreases in bone mineral density.[16 19]

All 15 studies reported data in relation to the risk of serious adverse events: 12 were placebo-controlled,[3 5 7 15-22 25] one compared PrEP with no PrEP[6], two compared tenofovir/emtricitabine with tenofovir[19 23] and one compared different dosage schedules.[24] A meta-analysis of placebo-controlled trials did not find an increased risk (RR 0.91, 95% CI: 0.74 to 1.13; I^2 = 67%, Figure S9, Supplementary Material 3.3).

In the only trial that compared PrEP with no treatment, an increased rate of serious adverse events was noted in the treatment arm (RR 3.42; 95% CI 1.4 to 8.35).[6] However, these adverse events were not considered study drug-related. Two studies compared tenofovir with tenofovir/emtricitabine: one found no significant difference between groups[23] and another found an increased rate in the tenofovir/emtricitabine group (RR 2.48; 95% CI: 1.42 to 4.33).[19] Of note, not all studies defined what constituted adverse events (including serious adverse events).

No study found an increased mortality rate associated with PrEP use, and of the deaths that occurred, none were considered to be drug-related (Figure S10, Supplementary Material 3.3).

Viral drug resistance mutations

Five placebo-controlled trials provided data on HIV mutations among patients who had acute HIV infection at enrolment (unknown to study investigators).[3 15 16 18 19] In total, there were 44 seroconversions at enrolment, 25 who received study drug and 19 who received placebo. There were nine mutations detected, eight among participants receiving study

drug and one in a patient receiving placebo. The RR for any drug mutation was 3.53 (95% CI: 1.18 to 10.56; I^2 = 0%, Figure S11, Supplementary Material 3.3) which represents a RD of 0.57 (95% CI: 0.21 to 0.94).

Of the nine resistance mutations at enrolment, seven were for emtricitabine. The RR for emtricitabine mutation was 3.72 (95% CI: 1.23 to 11.23; I^2 = 0%) which represents a RD of 0.6 (95% CI: 0.23 to 0.97) in those receiving tenofovir/emtricitabine (Figure S12, Supplementary Material 3.3).[3 16 18 19]

Among participants who seroconverted postrandomisation, the development of resistant mutations was uncommon. Of 551 seroconverters, only seven resistance mutations were detected; one tenofovir mutation was noted in a tenofovir-only arm (k65n, a rare tenofovir resistance mutation) and six emtricitabine mutations were noted.

Risk compensation

Changes in sexual behaviour, or 'risk compensation', was measured in a number of ways, including condom use, number of sexual partners, changes in STI rates and recreational drug use. Due to the differences in how sexual behaviour was reported across trials, including differing definitions and at different time points, a meta-analysis was not possible.

Studies consistently showed no between-group difference in condom use or number of sexual partners. Studies showed either no overall change in condom use throughout the duration of the study (n=4 studies) or an increase in condom use (n=4 studies). Most studies showed no change in the number of sexual partners over time (n=6 studies), four studies showed a slight reduction in number of sexual partners and one showed an increase (investigators of this study noted the possibility of partner underreporting at baseline[21]). No

study reported an increase in STIs or a between-group difference in STI diagnoses. In the only study to enroll intravenous drug users, a reduction in intravenous drug use, needle sharing and number of sexual partners over the course of the study was noted.[15] Supplementary Material 3.6 presents full details of behaviour change and STI rates in individual studies.

Discussion

Summary of findings

This systematic review and meta-analysis of 25,051 individuals encompassing 38,289 person-years of follow-up data confirms that oral tenofovir-containing PrEP is both effective and safe. PrEP is particularly effective in MSM, with a rate reduction of 75% across all trials, rising to 86% in trials with high adherence. Only one trial investigated the effectiveness of 'on demand' PrEP.[5] This trial reported a rate reduction of 86%, identical to the only comparable trial among daily PrEP users[6] (both trials enrolled a large sample of MSM and achieved high levels of adherence). PrEP is also effective in serodiscordant couples, and no significant difference exists between single-agent tenofovir and combination tenofovir/emtricitabine.

Questions remain regarding PrEP effectiveness in other populations. One study found that PrEP was effective in PWID.[15] However, a limitation of this study is that investigators were not sure if transmission was parenteral or sexual. It is unclear if PrEP is effective in heterosexuals. PrEP was effective in preventing heterosexual HIV transmission in one trial where adherence was high (61% reduction),[16] but only in male participants. The remaining three heterosexual trials, all conducted in sub-Saharan Africa, only enrolled females and adherence was noted to be very low.[7 17 19]

Adherence varied greatly across studies, ranging from 25% to 88% by plasma drug monitoring. As expected, efficacy was found to be strongly associated with adherence ($p<0.01$). On average, a 10% reduction in adherence reduced efficacy by 13%.

PrEP was found to be safe, and there was no difference in adverse event rates comparing single agent tenofovir with tenofovir/emtricitabine in combination. Some studies noted a

transient elevation of creatinine with resolution upon discontinuation of study drug.[3 5 6 15 18] While uncommon, viral drug resistance mutations may occur in the presence of an unrecognised HIV infection at enrolment.

Our findings of high effectiveness in MSM has been confirmed by two open-label extensions[26 27] that followed the conclusion of four RCTs included in this review.[3 5 20 25] One open-label extension found no seroconversions in participants that took a minimum of four pills per week.[26]

Ongoing studies

Following the conclusion of this review, an additional search was conducted to identify recently published or ongoing RCTs after the date of our database search. PubMed was searched, using the same search strategy, up to 9 September 2021. No additional PrEP efficacy trials were identified, although two publications were identified that relate to an ongoing non-inferiority RCT that compared two different types of oral tenofovir-containing PrEP: tenofovir alafenamide plus emtricitabine versus tenofovir disoproxil fumarate plus emtricitabine[28 29] (all studies in this systematic review relate to tenofovir disoproxil fumarate). Interim results found that the daily tenofovir alafenamide group showed non-inferior efficacy to the daily tenofovir disoproxil fumarate group for HIV prevention, and the number of adverse events for both regimens was low. Tenofovir alafenamide had more favourable effects on bone mineral density and biomarkers of renal safety than tenofovir disoproxil fumarate,[28] however there was more weight gain among participants who had received tenofovir alafenamide (median weight gain 1.7 kg vs 0.5 kg, p<0.0001).[29]

Strengths and limitations

This systematic review assessed the use of PrEP in all potentially eligible populations, and provided a GRADE assessment of important outcomes[999], ensuring a systematic and transparent approach in the development of national clinical practice guidelines for the prevention of HIV. Based on the strength of the evidence, this study was used to develop national clinical guidelines on the management of patients on PrEP,[30] and informed the decision of the Irish government to implement a publicly funded PrEP programme nationally for MSM and serodiscordant couples at increased risk, and for other populations on a case-by-case basis as determined by the treating HIV specialist.[31]

Despite the strength of the evidence, however, the present study is subject to a number of limitations. First, there was a lack of data on a number of other high risk groups, such as transgender women (only one study included transgender women, which made up less than 1% of participants[3]) and sex workers (one study included sex workers, however disaggregated data were not reported[17]). Second, adherence was notably poor in most studies that enrolled heterosexual women, limiting conclusions in this group. Additionally, as observational studies were excluded from this review, PrEP effectiveness may be lower in real-world settings in all populations if adherence is suboptimal. Third, while PrEP is considered to have an excellent safety profile, the maximum follow-up period was 6.9 years in this review and, therefore, long-term safety was not assessed.

Fourth, while studies in this review did not detect risk compensation, evidence from placebo-controlled trials is often insufficient to determine its presence. It is not possible to reach conclusions on the impact of PrEP on behaviour when participants do not know if they are taking active PrEP or placebo. However, it is possible to evaluate the impact of the support provided to all participants over time (provision of condoms, counselling on safer

sex practices). Studies generally demonstrated no change or an improvement in safer sex practices. In the open-label PROUD study (where participants knew they were taking PrEP), there was no difference between the immediate and deferred PrEP groups in the total number of sexual partners in the three months prior to the 1-year questionnaire.[6] However, a greater proportion of the immediate group reported receptive anal sex without a condom with 10 or more partners compared with the deferred group. Importantly, there was no difference in the frequency of bacterial STIs between groups, the most reliable proxy for changes in sexual behaviour (as it is not self-reported). Fifth, a number of studies in this review had zero events in one or both arms of the study. Standard meta-analytic approaches typically exclude these trials, resulting in a loss of data. A sensitivity analysis using alternative meta-analytic methods to account for these studies generally found similar findings, with the exception of the estimate of effectiveness in the 'low adherence' MSM group, which was no longer statistically significant.

Finally, the generalisability of studies to other clinical settings should be done with caution. All trials that enrolled heterosexuals were conducted in sub-Saharan Africa, a part of the world with a generalised HIV epidemic and suboptimal antiretroviral coverage. Additionally, the only trial that enrolled PWID was conducted in Bangkok, where needle exchange was unavailable to participants, and investigators could not differentiate sexually from parenterally acquired HIV.

Research in context and implications for practice

HIV infection is of significant public health importance. There were 523 diagnoses of HIV notified in 2018 in Ireland, representing a rate of 11 per 100,000 population, and over half (56%) of all diagnoses were in the MSM group.[32] The rate of HIV in Ireland is high compared

with other countries in Western Europe, many of which have seen declines in their HIV rates in recent years.[1] This highlights the ongoing need for newer, more effective prevention strategies to halt the transmission of HIV.

Our finding of high PrEP effectiveness among MSM concurs with other recent systematic reviews that focussed solely on the MSM population.[33 34] To our knowledge, this systematic review provides the first GRADE assessment of the totality of evidence across all populations that includes more recent trials with high adherence.[5 6] Our GRADE assessment differs significantly from that of Okwundu et al., published in 2012.[35]

Our quantification of the strength of the association between adherence and efficacy through meta-regression highlights the clinical importance of medication adherence support and counselling to prospective PrEP users. Additionally, our finding of emtricitabine resistance mutations occurring almost four times more often in those with acute HIV enrolment has implications for PrEP implementation going forward. Assessing if the patient could be in the 'window period' (the time between exposure to HIV and the point when HIV testing will give an accurate result) at enrolment is of critical importance, to ensure the patient is HIV negative prior to commencing PrEP. This highlights the need for PrEP delivery as part of a monitored programme that incorporates HIV testing and patient counselling on the risk and long-term consequences of resistance if poorly adherent to PrEP.

An additional finding of interest is the lack of significant difference in the effectiveness and safety of single agent tenofovir compared with combined tenofovir/emtricitabine. This may have implications for clinical practice, as tenofovir may be a suitable alternative for emtricitabine-allergic patients, and in resource-poor settings if cost or procurement of combination tenofovir/emtricitabine is an issue.

Conclusions

In conclusion, high-certainty evidence exists that PrEP is safe and, assuming adequate adherence, effectively prevents HIV in MSM and serodiscordant couples. One study found PrEP to be effective in PWID. The uncertainty regarding PrEP effectiveness in heterosexual individuals persists. Clinicians and policy-makers may decide to recommend PrEP to heterosexual individuals on a case-by-case basis, acknowledging adherence-related issues reported in trials. This review emphasises the importance of adherence support to ensure PrEP effectiveness is maintained, as well as the need for frequent HIV testing at enrolment and follow-up to avoid viral drug resistance mutations. Following the conclusion of this study, the Irish government implemented a publicly-funded PrEP programme for all individuals at increased risk of HIV acquisition, and developed national clinical practice guidelines for the provision of PrEP.

Author contributions: Dr. O Murchu: concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of paper for important intellectual content, statistical analysis. Mr. Marshall: acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of paper for important intellectual content. Dr. Teljeur: concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of paper for important intellectual content, statistical analysis, supervision. Dr. Harrington: concept and design, critical revision of paper for important intellectual content, analysis and interpretation of data, drafting of the manuscript, supervision. Dr. Hayes: concept and design, drafting of the manuscript, supervision. Dr. Moran: concept and design, drafting of the manuscript, supervision. Dr.

Ryan: concept and design, critical revision of paper for important intellectual content, drafting of the manuscript, supervision.

Competing interests: None declared.

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data sharing: All data relevant to the study are included in the article or uploaded as supplementary information.

Acknowledgements: The HSE's Sexual Health and Crisis Pregnancy Programme; the Gay Men's Health Centre Dublin; HIV Ireland; Act Up Dublin and the Gay Health Network.

References

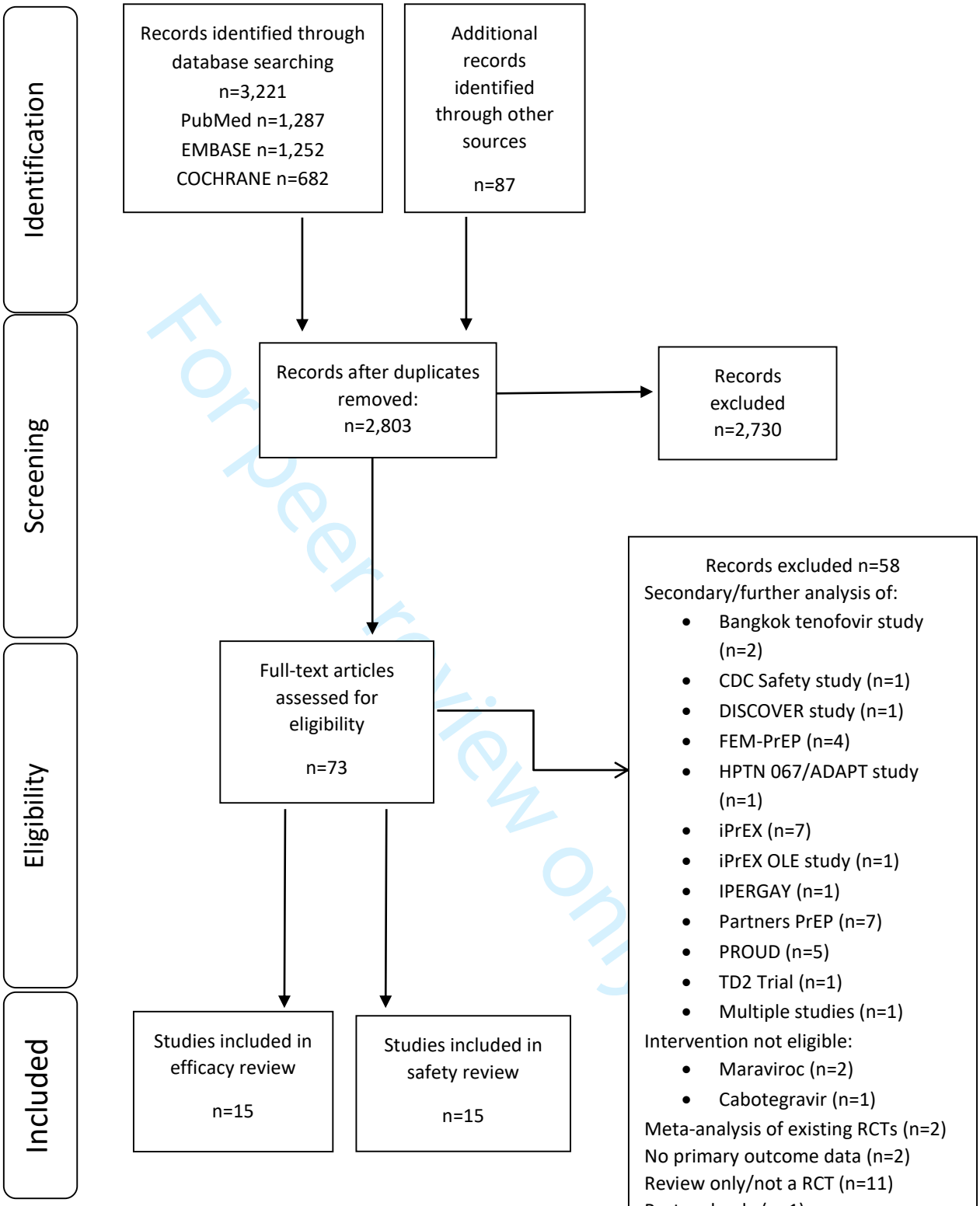
1. UNAIDS. Global HIV & AIDS statistics — 2020 fact sheet. Available at: https://www.unaids.org/en/resources/fact-sheet. Accessed 11.9.2021. 2020 [
2. WHO. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Available at: https://www.who.int/hiv/pub/guidelines/keypopulations/en/. Accessed 22.7.2019. 2014
3. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. 2010; 363(27).
4. WHO. WHO Expands Recommendation On Oral Preexposure Prophylaxis Of Hiv Infection (Prep). Available at: https://apps.who.int/iris/bitstream/handle/10665/197906/WHO_HIV_2015.48_eng.pdf;jsessionid=7B04813AFDE92D7F5EE3D71C8E921BBA?sequence=1. Accessed 22.7.2019. 2015
5. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *The New England journal of medicine* 2015;373(23):2237-46. doi: 10.1056/NEJMoa1506273 [published Online First: 2015/12/02]
6. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet (London, England)* 2016;387(10013):53-60. doi: 10.1016/s0140-6736(15)00056-2 [published Online First: 2015/09/14]
7. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *The New England journal of medicine* 2012;367(5):411-22. doi: 10.1056/NEJMoa1202614 [published Online First: 2012/07/13]
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339 doi: 10.1136/bmj.b2700
9. GRADE. The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) working group. Available at: http://www.gradeworkinggroup.org/.
10. Cochrane. The Cochrane Risk of Bias tool. Cochrane Handbook: Chapter 8. Available at: https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm.
11. Beisemann M, Doebler P, Holling H. Comparison of random-effects meta-analysis models for the relative risk in the case of rare events: A simulation study. *Biom J* 2020;62(7):1597-630. doi: 10.1002/bimj.201900379 [published Online First: 2020/06/09]
12. Chen Y, Hong C, Ning Y, et al. Meta-analysis of studies with bivariate binary outcomes: a marginal beta-binomial model approach. *Stat Med* 2016;35(1):21-40. doi: 10.1002/sim.6620 [published Online First: 2015/08/26]
13. Cheng J, Pullenayegum E, Marshall JK, et al. Impact of including or excluding both-armed zero-event studies on using standard meta-analysis methods for rare event outcome: a simulation study. *BMJ Open* 2016;6(8):e010983. doi: 10.1136/bmjopen-2015-010983
14. Rücker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Stat Med* 2008;27(5):746-63. doi: 10.1002/sim.2971 [published Online First: 2007/06/27]
15. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England)* 2013;381(9883):2083-90. doi: 10.1016/s0140-6736(13)61127-7 [published Online First: 2013/06/19]
16. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *New England journal of medicine* 2012; 367(5).

http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/265/CN-00840265/frame.html.
17. Peterson L, Taylor D, Roddy R, et al. Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial. *PLoS Clinical Trials* 2007;2(5):e27. doi: 10.1371/journal.pctr.0020027
18. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *New England journal of medicine* 2012; 367(5). http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/266/CN-00840266/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770474/pdf/nihms493581.pdf.
19. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *The New England journal of medicine* 2015;372(6):509-18. doi: 10.1056/NEJMoa1402269 [published Online First: 2015/02/05]
20. Grohskopf LA, Chillag KL, Gvetadze R, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *Journal of acquired immune deficiency syndromes (1999)* 2013;64(1):79-86. doi: 10.1097/QAI.0b013e31828ece33 [published Online First: 2013/03/08]
21. Mutua G, Sanders E, Mugo P, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. *Plos one* 2012; 7(4). http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/614/CN-00848614/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325227/pdf/pone.0033103.pdf.
22. Kibengo FM, Ruzagira E, Katende D, et al. Safety, adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. *PLoS One* 2013;8(9):e74314. doi: 10.1371/journal.pone.0074314 [published Online First: 2013/10/03]
23. Baeten JM, Donnell D, Mugo NR, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. *The lancet Infectious diseases* 2014; 14(11). http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/639/CN-01053639/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252589/pdf/nihms635147.pdf.
24. Bekker LG, Roux S, Sebastien E, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. *The lancet HIV* 2018;5(2):e68-e78. doi: 10.1016/s2352-3018(17)30156-x [published Online First: 2017/10/08]
25. Hosek SG, Siberry G, Bell M, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. *Journal of acquired immune deficiency syndromes (1999)* 2013;62(4):447-56. doi: 10.1097/QAI.0b013e3182801081 [published Online First: 2013/10/19]
26. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014;14(9):820-9. doi: 10.1016/s1473-3099(14)70847-3 [published Online First: 2014/07/30]
27. Molina JM CI, Spire B et al.,. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV 2017; 4: e402–e410. 2017
28. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-

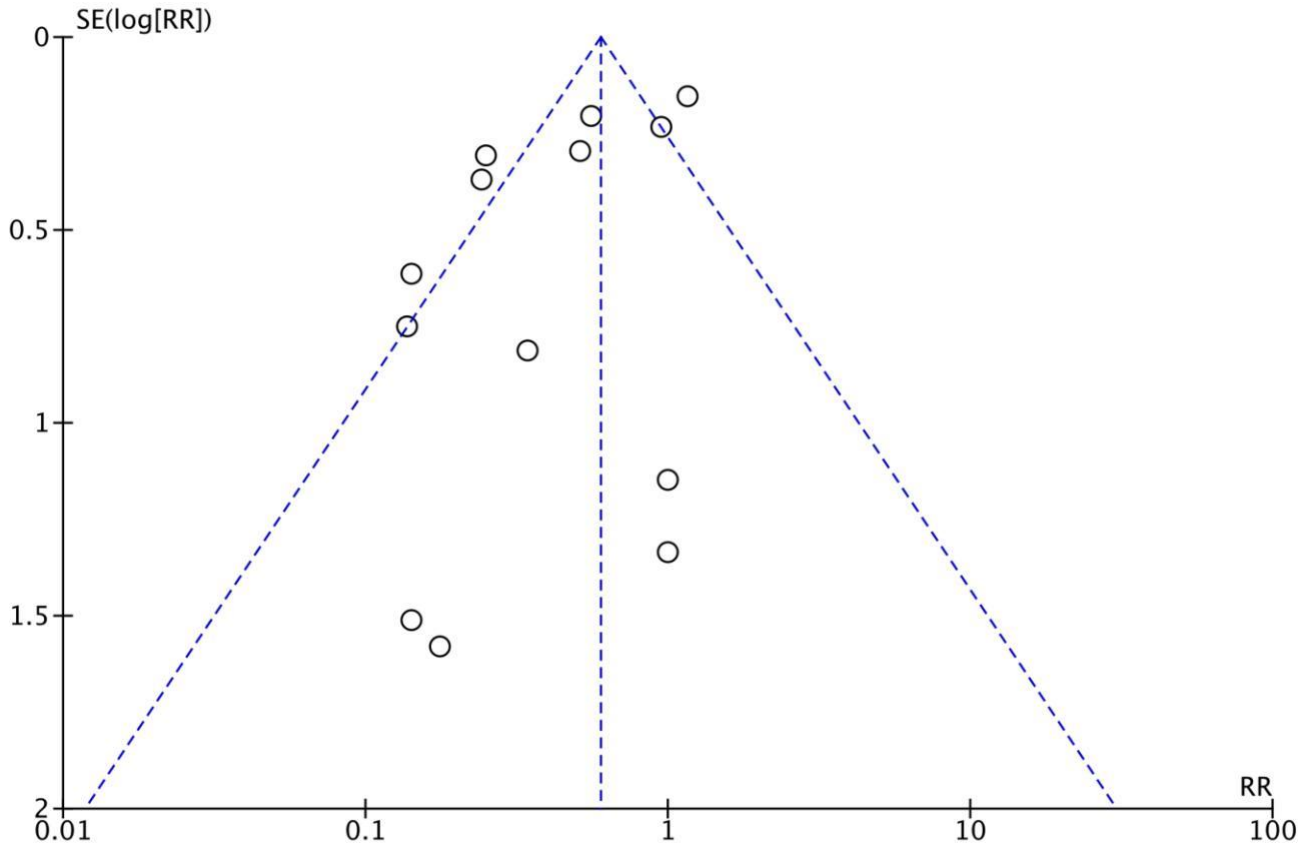
controlled, phase 3, non-inferiority trial. *Lancet (London, England)* 2020;396(10246):239 - 54. doi: 10.1016/S0140-6736(20)31065-5

29. Ogbuagu O, Ruane PJ, Podzamczer D, et al. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet HIV* 2021;8(7):e397-e407. doi: https://doi.org/10.1016/S2352-3018(21)00071-0
30. Health Service Executive (HSE). Clinical management guidance for individuals taking HIV PrEP within the context of a combination HIV (and STI) prevention approach in Ireland. PrEP clinical management guidance. Version 1.1. October 2019. Available at: https://www.sexualwellbeing.ie/for-professionals/prep-information-for-service-providers/guidelines-for-the-management-of-prep-in-ireland.pdf. Accessed 11.9.2021., 2019.
31. Department of Health. Taoiseach and Ministers for Health announce HIV PrEP programme: Press release. Published on 10 October 2019. 2019 [11.9.2021]. Available from: https://www.gov.ie/en/press-release/taoiseach-and-ministers-for-health-announce-hiv-prep-programme/.
32. Health Protection Surveillance Centre (HPSC). HIV in Ireland, 2018. Annual Epidemiological Report. Available at: https://www.hpsc.ie/a-z/hivandaids/hivdataandreports/HIV_2018_finalrev.pdf. Accessed 11.9.2021. 2019
33. Huang X, Hou J, Song A, et al. Efficacy and Safety of Oral TDF-Based Pre-exposure Prophylaxis for Men Who Have Sex With Men: A Systematic Review and Meta-Analysis. *Frontiers in pharmacology* 2018;9:799. doi: 10.3389/fphar.2018.00799 [published Online First: 2018/09/21]
34. Freeborn K, Portillo CJ. Does pre-exposure prophylaxis for HIV prevention in men who have sex with men change risk behaviour? A systematic review. *J Clin Nurs* 2018;27(17-18):3254-65. doi: 10.1111/jocn.13990
35. Okwundu CI, Uthman OA, Okoromah CAN. Antiretroviral pre - exposure prophylaxis (PrEP) for preventing HIV in high - risk individuals. *Cochrane Database of Systematic Reviews* 2012(7) doi: 10.1002/14651858.CD007189.pub3

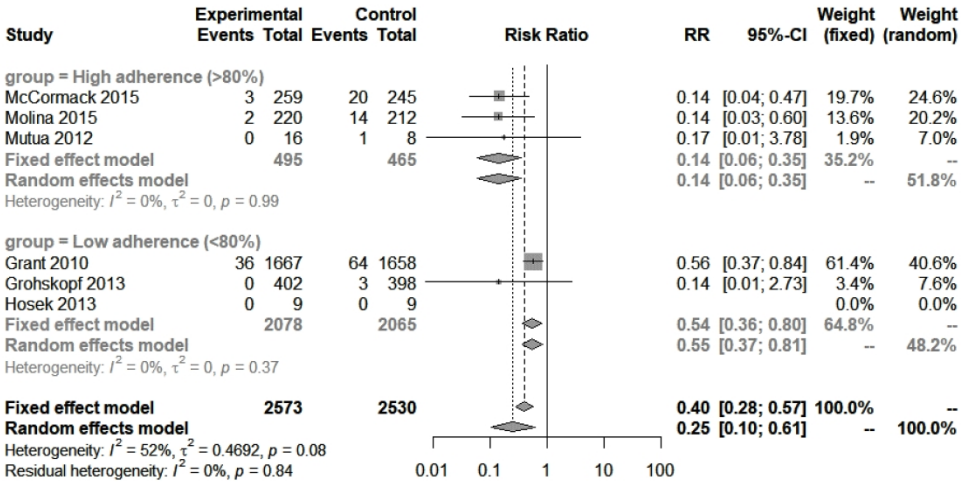
Figure 1. PRISMA diagram of study selection



Funnel plot (all studies)

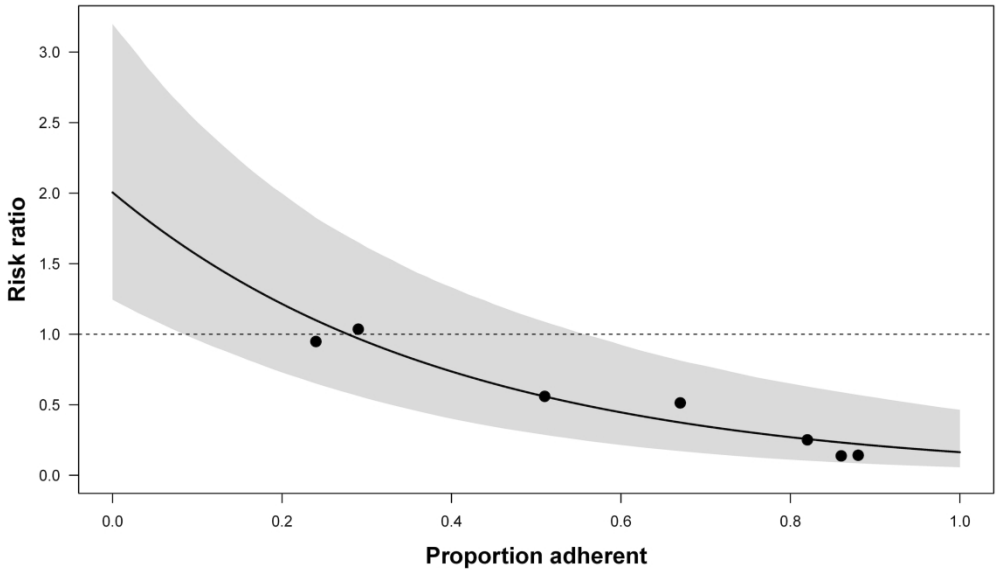


A funnel plot of all studies (n=13) is presented. There is no evidence of significant small study bias.



Caption : Forest plot of the meta-analysis of PrEP effectiveness in all MSM trials, PrEP versus placebo or no drug. Subgroups include high (≥80%) adherence and low (<80%) adherence. 'Events' refers to new HIV infections and 'Total' refers to total person-years at risk during the study period.

1055x529mm (118 x 118 DPI)



Caption : The X-axis represents the trial-level adherence as a proportion and the Y-axis represents the effectiveness as rate ratios. The solid line represents the fitted regression line and the shaded area the 95% Confidence Interval. Only studies that reported trial plasma drug concentrations contributed to analysis, represented as circles (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), VanDamme 2012 (FEM-PrEP). In the PROUD trial, adherence was only confirmed by plasma drug concentration in patients who reported taking PrEP (88%)

275x159mm (300 x 300 DPI)

Supplementary Material 1: Protocol

1. Background

Human Immunodeficiency Virus (HIV) persists as a significant public health threat. There were 511 HIV notifications in Ireland in 2016, giving a rate of 11.2 per 100,000. This is the highest rate ever reported in Ireland.[1] Men who have sex with men (MSM) remain the population most affected by HIV. In 2015, there were 247 new HIV diagnoses reported among MSM, just over half (51%) of all diagnoses in 2015. The number of diagnoses in 2015 was the highest number ever reported among MSM in Ireland and represents an increase of 34% compared to 2014.[1]

Pre-exposure prophylaxis (PrEP) is a biomedical HIV prevention strategy whereby oral anti-retrovirals (namely tenofovir-emtricitabine, Truvada®) are taken daily by HIV-negative individuals to prevent infection. In their latest guidelines, the World Health Organization (WHO) recommends that PrEP containing tenofovir disoproxil fumarate should be offered as part of HIV prevention programmes to people at 'substantial risk of HIV infection'.[2] Of note, PrEP offers no protection against sexually transmitted infections other than HIV.

In August 2016, the European Commission granted marketing authorisation for once-daily Truvada® in combination with safer-sex practices to reduce the risk of sexually acquired HIV-1 infection among uninfected adults at high risk. Therefore Truvada® is licensed for PrEP in Ireland.[3] However, it has not been made available through the Health Service Executive (HSE); no PrEP programme has been implemented and it is not reimbursed through the Primary Care Reimbursement Scheme.

2. Objective

To perform a systematic review of the efficacy of oral antiretroviral pre-exposure prophylaxis (PrEP) therapy to prevent HIV infection in all populations.

3. Methods

A systematic review of Randomised Controlled Trials (RCTs) will be performed. Systematic review will be registered with PROSPERO.

3.1 Criteria for considering studies for this review

Types of studies

RCTs that evaluated the efficacy of antiretroviral chemoprophylaxis in preventing HIV infection in men who have sex with men (MSM).

Types of participants

All populations at increased risk, including MSM transmission (males who have sex with males), transmission between serodiscordant sexual partners, heterosexual transmission, and people who inject drugs.

Types of interventions

Any oral tenofovir-based PrEP regimen.

Types of comparators

Placebo, no PrEP, or alternative medication/dosing schedule.

Types of outcome measures

Primary outcome:

Incidence of new HIV infections.

Secondary outcomes:

1. Adherence to PrEP (as measured by the primary studies)
2. Adverse events associated with PrEP (frequency and type of adverse effects or complications)
3. New STI infections
4. Behaviour change associated with PrEP administration (number of episodes of condomless anal intercourse and number of new sexual partners).

Table 1 outlines the PICOS criteria for inclusion of studies for inclusion.

Table 1: PICOS criteria

PICOS Criteria: Study Selection	
Population	Males who have sex with males, heterosexuals at increased risk, serodiscordant couples, people who inject drugs
Intervention	Pre-exposure prophylaxis (any oral antiretroviral formulation)
Comparator	Placebo, no treatment or alternative medication/dosage schedule
Outcomes	**Primary outcome:** HIV incidence **Secondary outcomes:** 1. Adherence to PrEP (as measured by the primary studies)

	2. Adverse events associated with PrEP (frequency and type of adverse effects or complications) 3. New STI infections 4. Behaviour change reported in RCTs associated with PrEP administration (episodes of condomless anal intercourse and number of new sexual partners)
Studies	Randomised Controlled Trials

3.2 Search methods for identification of studies

Electronic searches

Electronic searches will be conducted in Medline (PubMed), Embase and the Cochrane Register of Controlled Trials. Additional searches will include the CRD DARE Database, Morbidity and Mortality Weekly Report (CDC), Eurosurveillance reports and hand-searching of journals. The WHO International Clinical Trials Registry Platform and ClinicalTrials.gov will be searched for ongoing or prospective trials.

No restrictions will be placed based on location of the intervention. No language restrictions will be used. Articles in languages other than English will be translated where necessary.

The detailed search strategies for each of the databases MEDLINE via PubMed, EMBASE and The Cochrane Central Register of Controlled Trials are as follows:

Table 2: PubMed search strategy

PubMed Search	Queries
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR HIV[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR HIV infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]
#2	Search pre-exposure prophylaxis[tiab] OR preexposure prophylaxis[tiab] OR PREP[tiab] OR anti-retroviral chemoprophylaxis[tiab] OR antiretroviral chemoprophylaxis[tiab] OR chemoprevention[mh] OR chemoprevention[tiab] OR HIV prophylaxis[tiab]
#3	Search tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil
#4	#2 OR #3
#5	#1 AND #4 AND Filters: Clinical Trial, Randomized Controlled Trial, from 1000/1/1 - 2020/7/5

Table 3: Cochrane Central register search strategy

ID	Search
#1	MeSH descriptor HIV Infections explode all trees

#2	MeSH descriptor HIV explode all trees
#3	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME
#4	MeSH descriptor Sexually Transmitted Diseases, Viral, this term only
#5	(#1 OR #2 OR #3 OR #4)
#6	MeSH descriptor Chemoprevention explode all trees
#7	pre-exposure prophylaxis:ti,ab,kw OR preexposure prophylaxis:ti,ab,w OR PREP:ti,ab,kw OR anti-retroviral chemoprophylaxis:ti,ab,kw OR antiretroviral chemoprophylaxis:ti,ab,kw OR hiv prophylaxis:ti,ab,kw
#8	(#6 OR #7)
#9	tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil
#10	(#8 OR #9)
#11	(#5 AND #10)

Table 4: Embase search strategy

No.	Query
#1	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection'/de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus'/de OR 'human immunodeficiency virus' OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab OR 'human immunedeficiency virus':ti OR 'human immunedeficiency virus':ab OR 'human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab OR 'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab OR 'acquired immunedeficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab
#2	random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over*:ti OR cross?over:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/de OR 'crossover procedure' OR 'double-blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/de OR 'single-blind procedure' OR 'randomised controlled trial'/de OR 'randomised controlled trial' OR allocat*:ti OR allocat*:ab
#3	'pre-exposure prophylaxis' OR 'preexposure prophylaxis' OR prep OR 'anti-retroviral chemoprophylaxis' OR 'antiretroviral chemoprophylaxis' OR 'chemoprevention'/syn OR 'hiv prophylaxis' OR 'chemoprophylaxis'/syn
#4	'tenofovir'/syn OR tnf OR Tenofovir OR 'pmpa'/syn OR 'viread'/syn OR 'emtricitabine'/syn OR emc OR 'truvada'/syn OR 'emtriva'/syn OR 'coviracil'/syn
#5	#3 OR #4
#6	#1 AND #2 AND #5

Searching other resources

The reference lists of all included studies will be also be searched.

3.3 Data collection

Two reviewers will independently read the titles, abstracts, and descriptor terms of the search output from the different databases to identify potentially eligible studies. Full text articles will be obtained for all citations identified as potentially eligible. Both reviewers will independently inspect these to establish the relevance of the articles according to the pre-specified criteria. Studies will be reviewed for relevance based on study design, types of participants, interventions, and outcome measures. Reasons for excluding potentially relevant studies will be provided in an excluded studies table.

3.4 Data extraction and management

Data will be independently extracted using an agreed pro forma. Both reviewers will verify the extracted data. Extracted information will include the following:

- Study details: citation, study design and setting, time period and source of funding.
- Participant details: study population demographics, risk characteristics, population size and attrition rate.
- Intervention details: type of drug, comparator, dose, duration and route of administration.
- Outcome details: incidence of HIV infection (including type of laboratory tests used to confirm HIV diagnosis before and after administering PrEP), degree of adherence to PrEP, adverse effects, other STI infections.

RevMan software will be used to record extracted data. The reviewers will independently extract the data and enter them into RevMan; all entries will be rechecked by both reviewers, and all disagreements will be resolved by discussion. If results are pooled, a random effects meta-analysis, using the Mantel-Haenzel rate ratio, will be employed. Table 5 summarises the data collection, management and analysis.

Table 5: Data Collection, Management & Analysis

Data Collection and Management

Selection of studies	• Citations will be screened by one reviewer to eliminate clearly irrelevant studies • Two people will independently review the remaining citations per the inclusion criteria • Any disagreements will be resolved by discussion, or if necessary a third reviewer
Data extraction and management	• Data extraction will be performed independently onto a data extraction pro forma by two people • Any disagreements will be resolved by discussion or a third reviewer • RevMan software will be used to record extracted data
Assessment of risk of bias in included studies	• Risk of bias will be assessed using the Cochrane Risk of Bias Tool for RCTs • This will be performed by two people independently, with any disagreement being resolved by discussion or a third party • Small study bias will be assessed using a funnel plot and Egger's test • An overall assessment of the quality of the evidence will be assessed using the GRADE approach†
Measures of treatment effect and data synthesis	• Effect sizes will be expressed as the reduction in relative risk (RR) of HIV infection in the treatment group compared to control • A meta-analysis will be performed to provide a pooled risk if there is sufficient homogeneity across studies (all statistical analysis will be performed in R) • If significant heterogeneity is observed, a narrative metasynthesis will be performed.
Assessment of heterogeneity	• Clinical heterogeneity will be assessed by the reviewers based on the description of the interventions in the RCTs • Statistical heterogeneity will be examined using the I^2 statistic.

†The Cochrane Handbook. Section 12.2.1: The GRADE approach. Available at: http://handbook.cochrane.org/chapter_12/12_2_1_the_grade_approach.htm. Accessed May 2017.

3.5 Assessment of risk of bias in included studies

Two reviewers will independently examine the components of each included trial for risk of bias using a standard form. The Cochrane Risk of Bias tool will be employed. This will include information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the studies will be assessed and classified as adequate, inadequate or unclear as per the Cochrane Handbook of Systematic Reviews of Interventions. Where differences arise, they will be resolved by discussions with the third reviewer.

Table 6 outlines the potential risks of bias that will be assessed in included studies.

Table 6: Risk of Bias

Risk of Bias

Sequence generation	• Adequate: investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelope shuffling, etc. • Inadequate: investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number. • Unclear: insufficient information to permit judgement of the sequence generation process.
Allocation concealment	• Adequate: participants and the investigators enrolling participants cannot foresee assignment (e.g. central allocation; or sequentially numbered, opaque, sealed envelopes). • Inadequate: participants and investigators enrolling participants can foresee upcoming assignment (e.g. an open random allocation schedule (e.g. a list of random numbers); or envelopes were unsealed or nonopaque or not sequentially numbered). • Unclear: insufficient information to permit judgement of the allocation concealment or the method not described
Blinding	• Adequate: blinding of the participants, key study personnel and outcome assessor, and unlikely that the blinding could have been broken. Or lack of blinding unlikely to introduce bias. No blinding in the situation where non-blinding is not likely to introduce bias. • Inadequate: no blinding, incomplete blinding and the outcome is likely to be influenced by lack of blinding. • Unclear: insufficient information to permit judgement of adequacy or otherwise of the blinding.
Incomplete outcome data	• Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups. • Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data. • Unclear: insufficient reporting of attrition or exclusions.
Selective Reporting	• Adequate: a protocol is available which clearly states the primary outcome as the same as in the final trial report. • Inadequate: the primary outcome differs between the protocol and final trial report. • Unclear: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.
Other sources of bias	• Adequate: there is no evidence of bias from other sources. • Inadequate: there is potential bias present from other sources (e.g. early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design).

An overall assessment of the quality of the evidence will be assessed using the GRADE approach (the Cochrane Handbook, Section 12.2.1: The GRADE approach).

3.6 Measures of treatment effect

Outcome measures for dichotomous data (e.g., rate of HIV infection comparing intervention and comparator groups) will be calculated as a rate ratio (RR) with 95% confidence intervals (CI). A meta-analysis will be performed to provide a pooled risk if there is sufficient homogeneity across studies (all statistical analysis will be performed in Review Manager and R).

3.7 Dealing with missing data

Study authors will be contacted to provide further information on the results.

3.8 Assessment of heterogeneity

Clinical heterogeneity will be assessed by the reviewers based on the description of the interventions in the RCTs. Statistical heterogeneity will be examined using the I^2 statistic.

3.9 Subgroup analysis

Subgroup analyses by population group and adherence will be performed in the estimation of effectiveness.

3.10 Reporting guidelines

Reporting will adhere to the PRISMA guidelines for systematic reviews.[6]

References

1. HIV in Ireland 2016 Report. HPSC, HSE and UCD. Available at: https://www.hpsc.ie/a-z/hivandaids/hivdataandreports/2016reports/HIVIreland_2016.pdf.

2. WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015. Available at: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf. Accessed May 2017.

3. Truvada: EPAR. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/truvada

4. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339 doi: 10.1136/bmj.b2700

Supplementary Material 2

Database search – PubMed search strategy

PubMed

Search	Most Recent Queries	Citations
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR HIV[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR HIV infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]	413,629
#2	Search pre-exposure prophylaxis[tiab] OR preexposure prophylaxis[tiab] OR PREP[tiab] OR anti-retroviral chemoprophylaxis[tiab] OR antiretroviral chemoprophylaxis[tiab] OR chemoprevention[mh] OR chemoprevention[tiab] OR HIV prophylaxis[tiab]	35,711
#3	Search tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil	189,421
#4	#2 OR #3	224,005
#5	#1 AND #4 AND Filters: Clinical Trial, Randomized Controlled Trial, from 1000/1/1 - 2020/7/5	1,287

Supplementary Material 3: Additional Results

S3.1 List of included and excluded studies (with reasons)

S3.2 Risk of Bias assessment

S3.3 Additional figures and forest plots

S3.4 Results from Thigpen 2012 (by gender)

S3.5 Adherence

S3.6 Change in sexual behaviour/STI rates

S3.1

List of studies included in review

1. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. New England journal of medicine [Internet]. 2012; 367(5):[399-410 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/266/CN-00840266/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770474/pdf/nihms493581.pdf.

2. Baeten JM, Heffron R, Kidoguchi L, Mugo NR, Katabira E, Bukusi EA, et al. Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1–serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda. PLOS Medicine. 2016;13(8):e1002099.

3. Bekker LG, Roux S, Sebastien E, Yola N, Amico KR, Hughes JP, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. The lancet HIV. 2018;5(2):e68-e78.

4. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet (London, England). 2013;381(9883):2083-90.

5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New England journal of medicine [Internet]. 2010; 363(27):[2587-99 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/306/CN-00771306/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079639/pdf/nihms264954.pdf.

6. Grohskopf LA, Chillag KL, Gvetadze R, Liu AY, Thompson M, Mayer KH, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. Journal of acquired immune deficiency syndromes (1999). 2013;64(1):79-86.

7. Hosek SG, Siberry G, Bell M, Lally M, Kapogiannis B, Green K, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. Journal of acquired immune deficiency syndromes (1999). 2013;62(4):447-56.

8. Kibengo FM, Ruzagira E, Katende D, Bwanika AN, Bahemuka U, Haberer JE, et al. Safety,

adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. PLoS One. 2013;8(9):e74314.

9. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2015;372(6):509-18.

10. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet (London, England). 2016;387(10013):53-60.

11. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. The New England journal of medicine. 2015;373(23):2237-46.

12. Mutua G, Sanders E, Mugo P, Anzala O, Haberer JE, Bangsberg D, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. Plos one [Internet]. 2012; 7(4):[e33103 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/614/CN-00848614/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325227/pdf/pone.0033103.pdf.

13. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial. PLoS Clinical Trials. 2007;2(5):e27.

14. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. New England journal of medicine [Internet]. 2012; 367(5):[423-34 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/265/CN-00840265/frame.html.

15. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2012;367(5):411-22.

List of studies excluded from review

1. Agot K, Taylor D, Corneli AL, Wang M, Ambia J, Kashuba AD, et al. Accuracy of Self-Report and Pill-Count Measures of Adherence in the FEM-PrEP Clinical Trial: Implications for Future HIV-Prevention Trials. AIDS and behavior. 2015;19(5):743-51. [reason: secondary analysis of FEM-PrEP]

2. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Science translational medicine. 2012;4(151):151ra25. [reason: secondary analysis of iPrEX]

3. Baeten JM, Donnell D, Mugo NR, Ndase P, Thomas KK, Campbell JD, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. The lancet Infectious diseases [Internet]. 2014; 14(11):[1055-64 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/639/CN-01053639/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252589/pdf/nihms635147.pdf. [reason: duplicate]

4. Buchbinder SP, Glidden DV, Liu AY, McMahan V, Guanira JV, Mayer KH, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. The Lancet Infectious diseases. 2014;14(6):468-75. [reason: secondary analysis of iPrEX]

5. Buchbinder SP, Liu AY. CROI 2014: New tools to track the epidemic and prevent HIV infections. Topics in Antiviral Medicine. 2014;22(2):579-93. [reason: review; not a RCT]

6. Campbell JD, Herbst JH, Koppenhaver RT, Smith DK. Antiretroviral prophylaxis for sexual and injection drug use acquisition of HIV. American Journal of Preventive Medicine. 2013;44(1 SUPPL. 2):S63-S9. [reason: review, not a RCT]

7. Celum C, Baeten JM. Antiretroviral-based HIV-1 prevention: Antiretroviral treatment and pre-exposure prophylaxis. Antiviral Therapy. 2012;17(8):1483-93. [reason: review/not a RCT]

8. Corneli AL, Deese J, Wang M, Taylor D, Ahmed K, Agot K, et al. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. Journal of acquired immune deficiency syndromes (1999). 2014;66(3):324-31. [reason: secondary analysis of FEM-PrEP]

9. Corneli AL, McKenna K, Headley J, Ahmed K, Odhiambo J, Skhosana J, et al. A descriptive analysis of perceptions of HIV risk and worry about acquiring HIV among FEM-PrEP

participants who seroconverted in Bondo, Kenya, and Pretoria, South Africa. Journal of the International AIDS Society. 2014;17(3). [reason: secondary analysis of FEM-PrEP]

10. Deutsch MB, Glidden DV, Sevelius J, Keatley J, McMahan V, Guanira J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. The lancet HIV. 2015;2(12):e512-9. [reason: secondary analysis of iPrEX]

11. Dolling DI, Desai M, McOwan A, Gilson R, Clarke A, Fisher M, et al. An analysis of baseline data from the PROUD study: An open-label randomised trial of pre-exposure prophylaxis. Trials. 2016;17(1). [reason: secondary analysis of PROUD]

12. Dunn DT, Glidden DV. Statistical issues in trials of preexposure prophylaxis. Current Opinion in HIV and AIDS. 2016;11(1):116-21. [reason: review/not a RCT]

13. Elbirt D, Mahlab-Guri K, Bezalel-Rosenberg S, Asher I, Sthoeger Z. Pre-exposure prophylaxis as a method for prevention of human immunodeficiency virus infection. Israel Medical Association Journal. 2016;18(5):294-8. [reason: review, not a RCT]

14. Fidler S, Bock P. Prophylactic antiretroviral HIV therapy prevents infection in heterosexual men and women. Evidence-Based Medicine. 2013;18(5):184-5. [Reason: not a RCT, review of Baeten et al.]

15. Gilmore HJ, Liu A, Koester KA, Amico KR, McMahan V, Goicochea P, et al. Participant experiences and facilitators and barriers to pill use among men who have sex with men in the iPrEx pre-exposure prophylaxis trial in San Francisco. AIDS patient care and stds [Internet]. 2013; 27(10):[560-6 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/551/CN-00962551/frame.html. [reason: secondary analysis of iPrEX]

16. Grangeiro A, Couto MT, Peres MF, Luiz O, Zucchi EM, de Castilho EA, et al. Pre-exposure and postexposure prophylaxes and the combination HIV prevention methods (The Combine! Study): protocol for a pragmatic clinical trial at public healthcare clinics in Brazil. BMJ open. 2015;5(8):e009021. [reason: protocol]

17. Grant RM, Liegler T, Defechereux P, Kashuba AD, Taylor D, Abdel-Mohsen M, et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women. AIDS (London, England). 2015;29(3):331-7. [reason: not an efficacy RCT; further analysis of FEM-PrEP]

18. Gray RH, Wawer MJ. Infection in 2012: Mixed results of pre-exposure prophylaxis for HIV prevention. Nature Reviews Urology. 2013;10(2):74-5. [reason: review]

19. Gulick RM, Wilkin TJ, Chen YQ, Landovitz RJ, Amico KR, Young AM, et al. Phase 2 Study of the Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV

Infection in Men Who Have Sex With Men (HPTN 069/ACTG A5305). The Journal of infectious diseases. 2017;215(2):238-46. [reason: different intervention (maraviroc)]

20. Gulick RM, Wilkin TJ, Chen YQ, Landovitz RJ, Amico KR, Young AM, et al. Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV Infection in Women: A Phase 2 Randomized Trial. Annals of internal medicine. 2017;167(6):384-93. [reason: different intervention (maraviroc)]

21. Gust DA, Soud F, Hardnett FP, Malotte CK, Rose C, Kebaabetswe P, et al. Evaluation of Sexual Risk Behavior Among Study Participants in the TENOFOVIR2 PrEP Study Among Heterosexual Adults in Botswana. Journal of acquired immune deficiency syndromes (1999). 2016;73(5):556-63. [reason: secondary analysis of TD2 trial]

22. Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, et al. Adherence to Antiretroviral Prophylaxis for HIV Prevention: A Substudy Cohort within a Clinical Trial of serodiscordant Couples in East Africa. PLoS Medicine. 2013;10(9). [reason: secondary analysis of Partners PrEP]

23. Hanscom B, Janes HE, Guarino PD, Huang Y, Brown ER, Chen YQ, et al. Brief report: Preventing HIV-1 infection in women using oral preexposure prophylaxis: A meta-analysis of current evidence. Journal of Acquired Immune Deficiency Syndromes. 2016;73(5):606-8. [reason: meta-analysis of RCTs]

24. Jiang J, Yang X, Ye L, Zhou B, Ning C, Huang J, et al. Pre-exposure prophylaxis for the prevention of HIV infection in high risk populations: A meta-analysis of randomized controlled trials. PLoS ONE. 2014;9(2). [reason: meta-analysis of existing RCTs]

25. K RA, McMahan V, Goicochea P, Vargas L, Marcus JL, Grant RM, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. AIDS and behavior. 2012;16(5):1243-59. [reason: secondary analysis of iPrEX]

26. Koester KA, Liu A, Eden C, Amico KR, McMahan V, Goicochea P, et al. Acceptability of drug detection monitoring among participants in an open-label pre-exposure prophylaxis study. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2015;27(10):1199-204. [reason: observational study on subset of iPrEX OLE study]

27. Koss CA, Bacchetti P, Hillier SL, Livant E, Horng H, Mgodi N, et al. Differences in Cumulative Exposure and Adherence to Tenofovir in the VOICE, iPrEx OLE, and PrEP Demo Studies as Determined via Hair Concentrations. AIDS Research and Human Retroviruses. 2017;33(8):778-83. [reason: secondary analysis of 3 studies]

28. Lehman DA, Baeten JM, McCoy CO, Weis JF, Peterson D, Mbara G, et al. Risk of drug resistance among persons acquiring HIV within a randomized clinical trial of single-or

dual-agent preexposure prophylaxis. Journal of Infectious Diseases. 2015;211(8):1211-8. [reason: secondary analysis of Partners PrEP study]

29. Liu A, Glidden DV, Anderson PL, Amico KR, McMahan V, Mehrotra M, et al. Patterns and correlates of PrEP drug detection among MSM and transgender women in the global iPrEx study. Journal of Acquired Immune Deficiency Syndromes. 2014;67(5):528-37. [reason: secondary analysis of iPrEX]

30. Liu AY, Vittinghoff E, Chillag K, Mayer K, Thompson M, Grohskopf L, et al. Sexual risk behavior among HIV-uninfected men who have sex with men participating in a tenofovir preexposure prophylaxis randomized trial in the United States. Journal of acquired immune deficiency syndromes (1999). 2013;64(1):87-94. [reason: secondary analysis of US CDC Safety Study]

31. Lorente N, Fugon L, Carrieri MP, Andreo C, Le Gall JM, Cook E, et al. Acceptability of an on-demand pre-exposure HIV prophylaxis trial among men who have sex with men living in France. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2012;24(4):468-77. [reason: acceptability study prior to RCT]

32. Markowitz M, Frank I, Grant RM, Mayer KH, Elion R, Goldstein D, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. The lancet HIV. 2017;4(8):e331-e40. [reason: intervention different (cabotegravir)]

33. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Chuachoowong R, Mock PA, et al. Enrollment characteristics and risk behaviors of injection drug users participating in the Bangkok Tenofovir Study, Thailand. PLoS One. 2011;6(9):e25127. [reason: secondary analysis of Bangkok tenofovir study enrolment characteristics]

34. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Risk behaviors and risk factors for HIV infection among participants in the Bangkok tenofovir study, an HIV pre-exposure prophylaxis trial among people who inject drugs. PLoS One. 2014;9(3):e92809. [reason: secondary analysis of Bangkok tenofovir study enrolment characteristics]

35. McCormack SM, Noseda V, Molina JM. PrEP in Europe - Expectations, opportunities and barriers. Journal of the International AIDS Society. 2016;19. [reason: not a RCT; review article]

36. Mehrotra ML, Westreich D, McMahan VM, Glymour MM, Geng E, Grant RM, et al. Baseline Characteristics Explain Differences in Effectiveness of Randomization to Daily Oral TDF/FTC PrEP Between Transgender Women and Cisgender Men Who Have Sex With Men in the iPrEx Trial. Journal of acquired immune deficiency syndromes (1999).

2019;81(3):e94-e8. Epub 2019/06/14. doi: 10.1097/qai.0000000000002037. [reason: secondary analysis iPrEX]

37. Mills A, Workowski K, Campbell T, Benson P, Crofoot G, Salazar L, et al. Renal outcomes for participants taking F/TAF vs. F/TDF for HIV PrEP in the DISCOVER trial. Open Forum Infectious Diseases. 2019;6:S64. doi: 10.1093/ofid/ofz359.139. [reason: review; no efficacy data]

38. Miltz AR, Lampe FC, Bacchus LJ, McCormack S, Dunn D, White E, et al. Intimate partner violence, depression, and sexual behaviour among gay, bisexual and other men who have sex with men in the PROUD trial. BMC public health. 2019;19(1):431. Epub 2019/04/27. doi: 10.1186/s12889-019-6757-6.. [reason: secondary analysis PROUD]

39. Mugwanya KK, Donnell D, Celum C, Thomas KK, Ndase P, Mugo N, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis. The lancet Infectious diseases [Internet]. 2013; 13(12):[1021-8 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/297/CN-00915297/frame.html. [reason: longitudinal analysis of Partners PrEP]

40. Mujugira A, Baeten JM, Donnell D, Ndase P, Mugo NR, Barnes L, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. Plos one [Internet]. 2011; 6(10):[e25828 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/232/CN-00805232/frame.html. [reason: secondary analysis Partners PrEP]

41. Murnane PM, Brown ER, Donnell D, Coley RY, Mugo N, Mujugira A, et al. Estimating Efficacy in a Randomized Trial With Product Nonadherence: Application of Multiple Methods to a Trial of Preexposure Prophylaxis for HIV Prevention. American Journal of Epidemiology. 2015;182(10):848-56. [reason: secondary analysis Partners PrEP]

42. Murnane PM, Celum C, Mugo N, Campbell JD, Donnell D, Bukusi E, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS (london, england) [Internet]. 2013; 27(13):[2155-60 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/174/CN-01000174/frame.html. [reason: secondary analysis Partners PrEP]

43. Ndase P, Celum C, Campbell J, Bukusi E, Kiarie J, Katabira E, et al. Successful discontinuation of the placebo arm and provision of an effective HIV prevention product after a positive interim efficacy result: the partners PrEP study experience. Journal of acquired immune deficiency syndromes (1999) [Internet]. 2014; 66(2):[206-12 pp.]. Available from: http://cochranelibrary-

wiley.com/o/cochrane/clcentral/articles/717/CN-00992717/frame.html. [reason: review of Partners PrEP]

44. O'Halloran C, Rice B, White E, Desai M, D TD, McCormack S, et al. Chemsex is not a barrier to self-reported daily PrEP adherence among PROUD study participants. International Journal of Drug Policy. 2019;74:246-54. doi: 10.1016/j.drugpo.2019.10.007 [reason: secondary analysis PROUD]

45. Page K, Tsui J, Maher L, Choopanya K, Vanichseni S, Philip Mock M, et al. Biomedical HIV prevention including pre-exposure prophylaxis and opiate agonist therapy for women who inject drugs: State of research and future directions. Journal of Acquired Immune Deficiency Syndromes. 2015;69:S169-S75. [reason: review; not a RCT]

46. Post F, Spinner C, Coll P, Hawkins T, Anderson J, Zhong L, et al. DISCOVER in Europe: A sub-analysis of the phase 3 randomized, controlled trial of daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP). HIV Medicine. 2019;20:243-4. doi: 10.1111/hiv.12815. [reason: abstract only/no full text available]

47. Roux P, Fressard L, Suzan-Monti M, Chas J, Sagaon-Teyssier L, Capitant C, et al. Is on-Demand HIV Pre-exposure Prophylaxis a Suitable Tool for Men Who Have Sex With Men Who Practice Chemsex? Results From a Substudy of the ANRS-IPERGAY Trial. Journal of acquired immune deficiency syndromes (1999). 2018;79(2):e69-e75. Epub 2018/09/14. doi: 10.1097/qai.0000000000001781. [reason: secondary analysis IPERGAY]

48. Ruane PJ, Clarke A, Post FA, Schembri G, Jessen H, Trottier B, et al. Phase 3 randomized, controlled DISCOVER study of daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP): Week 96 results. HIV Medicine. 2019;20:95-6. doi: 10.1111/hiv.12815. [reason: abstract only/no full text available]

49. Sacks HS. Preexposure tenofovir-emtricitabine reduced HIV infection in men who have unprotected anal sex with men. Annals of Internal Medicine. 2016;164(2):JC3. [reason: review of PROUD]

50. Spinner CD, Brunetta J, Shalit P, Prins M, Cespedes M, Brainard D, et al. DISCOVER study for HIV pre-exposure prophylaxis (PrEP): F/TAF has a more rapid onset and longer sustained duration of HIV protection compared with F/TDF. Journal of the International AIDS Society. 2019;22. doi: 10.1002/jia2.25327. [reason: abstract only/no full text available]

51. Thomson KA, Baeten JM, Mugo NR, Bekker LG, Celum CL, Heffron R. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. Current Opinion in HIV and AIDS. 2016;11(1):18-26. [reason: review; not a RCT]

52. Velloza J, Bacchetti P, Hendrix CW, Murnane P, Hughes JP, Li M, et al. Short- and Long-Term Pharmacologic Measures of HIV Pre-exposure Prophylaxis Use Among High-Risk Men Who Have Sex With Men in HPTN 067/ADAPT. Journal of acquired immune deficiency syndromes (1999). 2019;82(2):149-58. Epub 2019/07/25. doi: 10.1097/qai.0000000000002128. [reason: secondary analysis HPTN 067/ADAPT]

53. Vermund SH. Safety and tolerability of tenofovir for preexposure prophylaxis among men who have sex with men. Journal of Acquired Immune Deficiency Syndromes. 2013;64(1):3-6. [reason: review; not a RCT]

54. White E, Dunn DT, Desai M, Gafos M, Kirwan P, Sullivan AK, et al. Predictive factors for HIV infection among men who have sex with men and who are seeking PrEP: a secondary analysis of the PROUD trial. Sexually transmitted infections. 2019;95(6):449-54. Epub 2019/03/29. doi: 10.1136/sextrans-2018-053808.. [reason: secondary analysis PROUD]

55. Wohl D, Ruane P, Hosek S, Creticos C, Morris S, Phoenix J, et al. Bone safety outcomes with F/TAF vs. F/TDF for PrEP in the DISCOVER trial. Open Forum Infectious Diseases. 2019;6:S464. doi: 10.1093/ofid/ofz360.1151. [reason: review; no efficacy data]

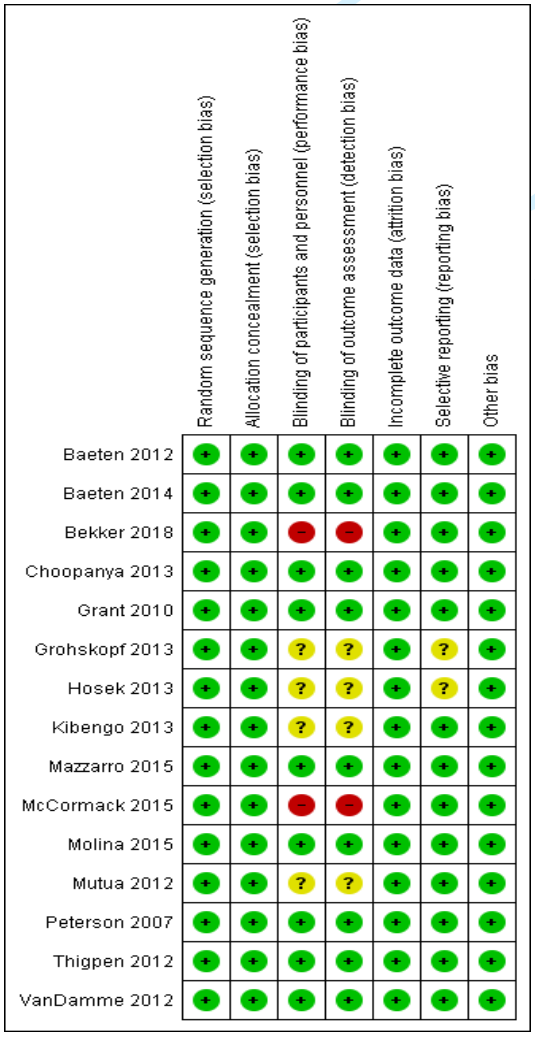
56. Yacoub R, Nadkarni GN, Weikum D, Konstantinidis I, Boueilh A, Grant RM, et al. Elevations in serum creatinine with tenofovir-based HIV pre-exposure prophylaxis: A meta-analysis of randomized placebo-controlled trials. Journal of Acquired Immune Deficiency Syndromes. 2016;71(4):e115-e8. [reason: meta-analysis of RCTs]

S3.2

Risk of Bias assessment

Two studies were open-label trials and, as such, blinding of participants or investigators was not possible. A further three studies were placebo-controlled trials that additionally investigated alternate dosing schedules; while participants and investigators were blinded to drug assignment, they could not be blinded to regimen assignment. One study contained a 'no pill' arm that could not be blinded in addition to a placebo arm. Two studies had unclear risk for reporting bias due to the fact that study protocols were not available. Figure S1 represents the review authors' judgements about each risk of bias item for each included study.

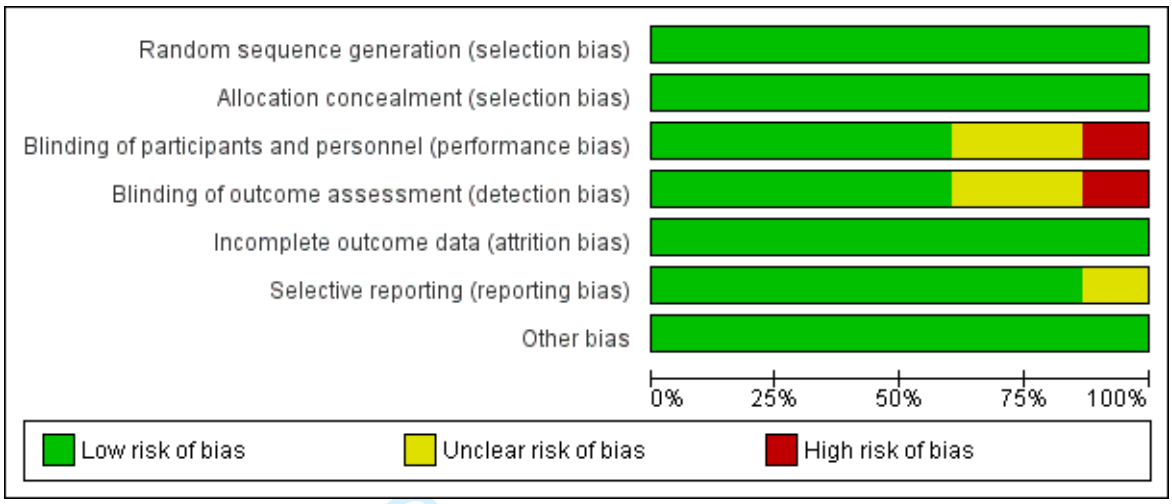
Figure S1. Risk of bias summary



Supplementary Material

Figure S2 represents the review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure S2. Risk of bias graph



S3.3 Additional figures and forest plots

Efficacy

Figure S3. Meta-analysis: HIV acquisition, all trials (PrEP versus placebo or no drug)

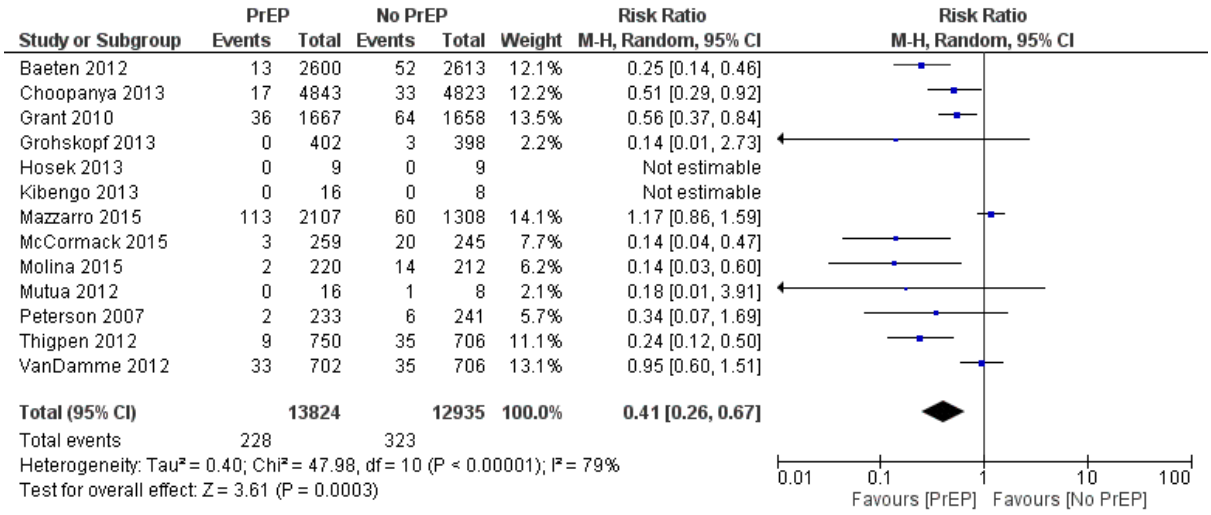


Figure S4. Meta-analysis: HIV acquisition in heterosexual participants, PrEP versus placebo, all trials

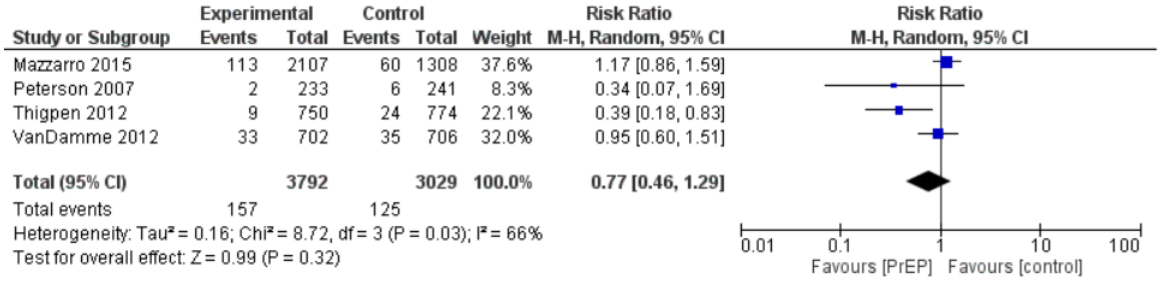
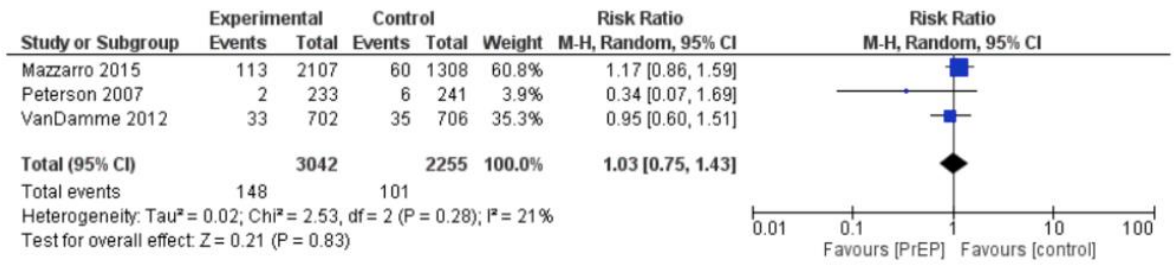


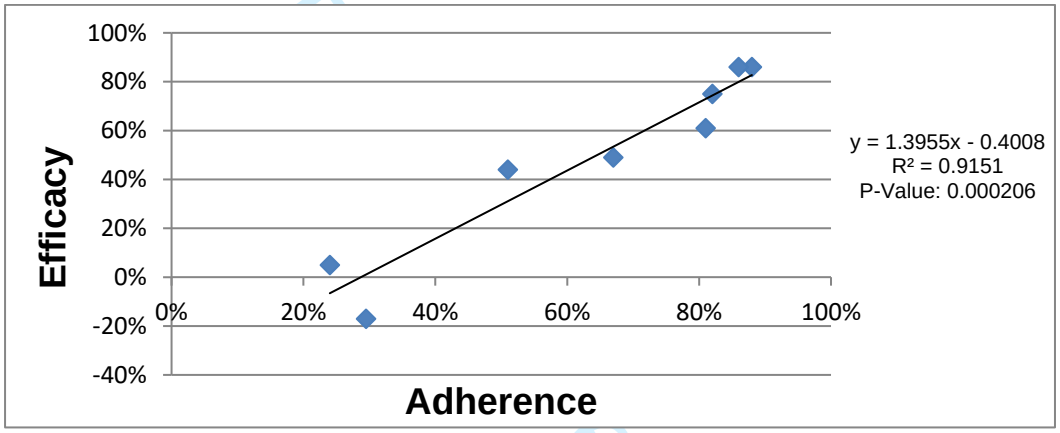
Figure S5. Meta-analysis: HIV acquisition in heterosexual participants, PrEP versus placebo, studies with low (<80%) adherence



Adherence

Figure S3 compares efficacy and adherence (measured by plasma drug concentration of participants, or plasma drug confirmation of self-reported adherence; n=7 trials). A regression model yielded a R^2 of 0.92 ($p<0.001$).

Figure S6. Efficacy as a function of adherence



Caption: Only trials that reported plasma drug concentrations contributed to anlaysis: (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), Thigpen 2012 (TDF2 study), VanDamme 2012 (FEM-PrEP)

Safety

Figure S7. Meta-analysis: 'any adverse event', PrEP versus placebo

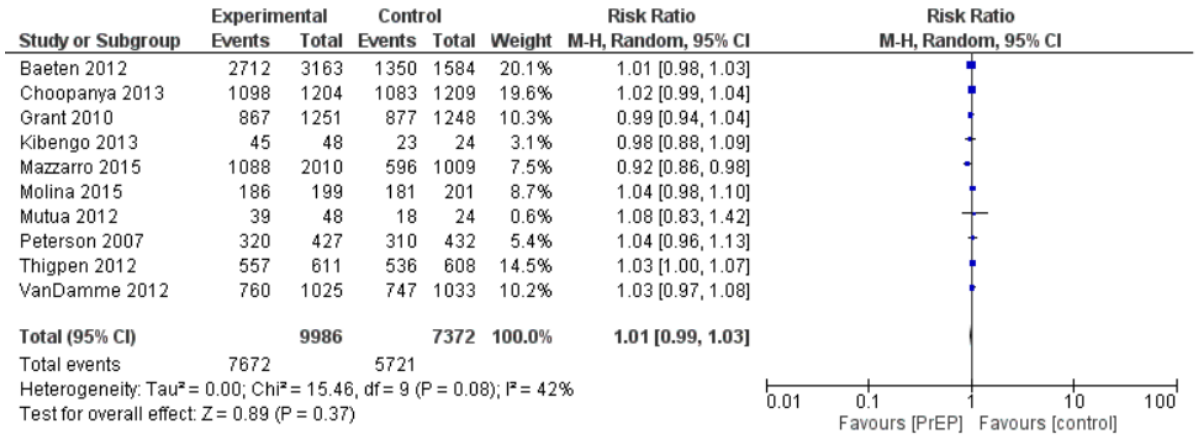


Figure S8. Meta-analysis: 'any adverse event', tenofovir/emtricitabine versus tenofovir

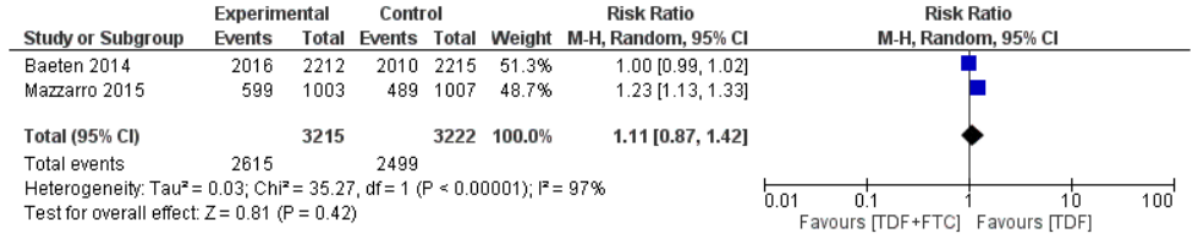
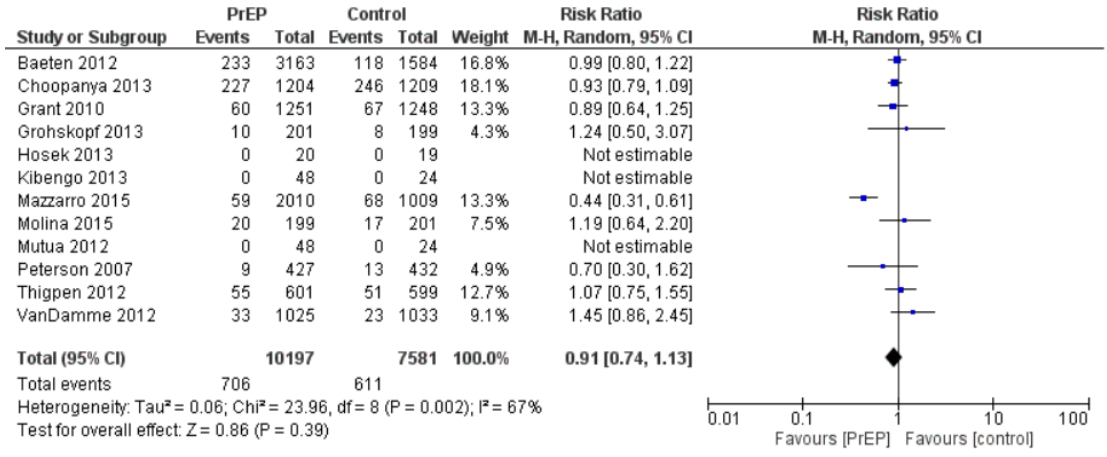
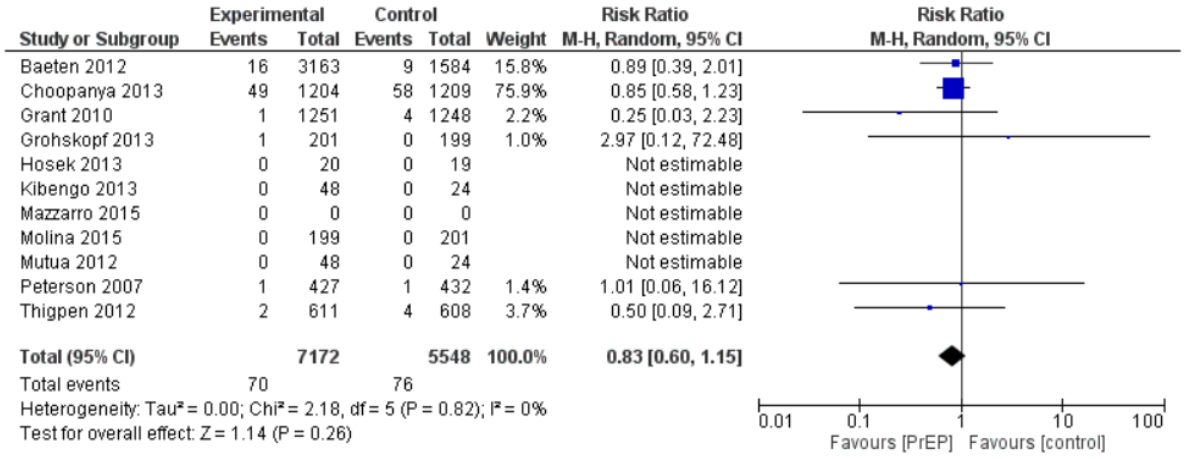


Figure S9. Meta-analysis: serious adverse events, PrEP versus placebo



Supplementary Material

Figure S10. Meta-analysis: deaths, PrEP versus placebo



Viral drug resistance mutations

Figure S11. Meta-analysis: any drug mutation (acute HIV at enrolment), PrEP versus placebo

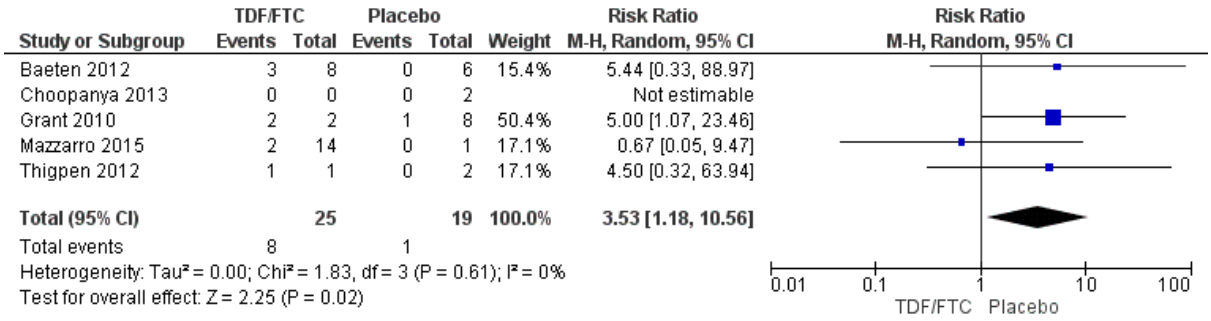
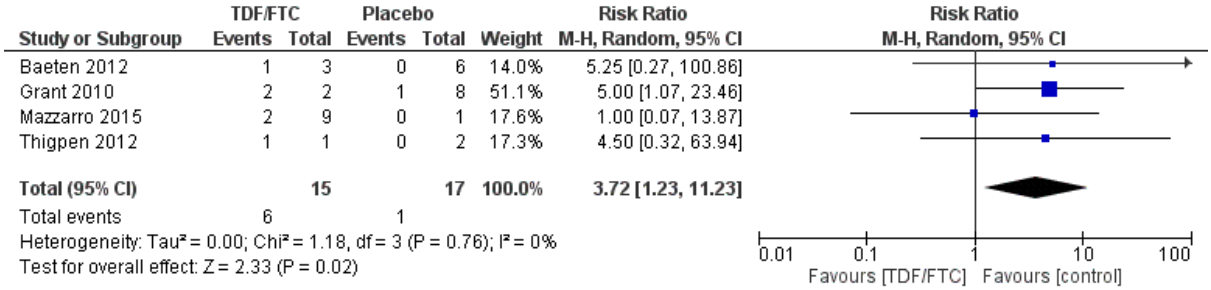


Figure S12. Meta-analysis: emtricitabine mutation (acute HIV at enrolment), tenofovir/emtricitabine versus placebo



S3.4

Results from Thigpen 2012 (by gender)

Number of HIV infections and PrEP efficacy by gender

	Tenofovir-emtricitabine group	Placebo group	Efficacy	95% CI	p-value
Female	7	14	49.4	-21.5, 80.8	0.11
Male	2	10	80.1	24.6, 96.9	0.03

Cohort is modified intention-to-treat; note that disaggregated data on overall number of male and female participants in each study arm not reported, precluding the evaluation of absolute risk.

S3.5 Adherence, as measured in primary studies

Study	Intervention	Adherence
Bekker 2018 (ADAPT Cape Town)	Tenofovir/emtricitabine (daily, time and event-driven PrEP)	• 75% (7,283 of 9,652 doses taken) for daily regimen; 65% (2,367 of 3,616 doses taken) for time-driven regimen and 53% (1,161 of 2,203 doses taken) for those event-driven regimen by electronic drug monitoring.
Baeten 2012 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (three arms: two active arms and one placebo arm)	• Factoring in missed visits, other reasons for non-dispensation of study medication and non-adherence to dispensed study pills, 92.1% of follow-up time was covered by study medication. • Among 29 subjects on the tenofovir and emtricitabine/tenofovir arms who acquired HIV-1, 31% had tenofovir detected in a plasma sample at the seroconversion visit compared with 82% of 902 samples from a randomly-selected subset of 198 subjects who did not acquire HIV-1.
Baeten 2014 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (two active arms)	• Study medication was taken by participants on 90.0% of days during follow-up time (factoring in protocol-defined study medication interruptions, missed visits, and non-adherence to dispensed study pills, as measured by monthly pill counts of returned study tablets). • Among subjects who acquired HIV-1, the minority (14/51, 27.5%) had tenofovir detected in a plasma sample at the visit at which HIV-1 seroconversion was detected, compared with the majority (1,047/1,334, 78.5%) of samples from a randomly selected subset of subjects who did not acquire HIV-1.
Choopanya 2013 (Bangkok Tenofovir Study)	Tenofovir (daily)	• Adherence was assessed daily at directly observed therapy (DOT) visits and monthly at non-DOT visits using a study drug diary. On the basis of participants' study drug diaries, participants took the study drug an average (mean) of 83.8% of days. • Plasma samples were obtained from 46 participants with incident HIV infections the day infection was detected, and from 282 HIV-negative participants to test for the presence of tenofovir. Tenofovir was detected in one (1%) of 177 participants in the placebo group and 100 (66%) of 151 participants in the tenofovir group. • In the case-control analysis in participants assigned to tenofovir, tenofovir was detected in the plasma of 5 (39%) of 13 HIV-positive participants and 93 (67%) of 138 HIV-negative participants.
Grant 2010 (iPrEx)	Tenofovir/emtricitabine (daily)	• The rate of self-reported pill use was lower in the emtricitabine–tenofovir group than in the placebo group at week 4 (mean, 89% vs. 92%) and at week 8 (mean, 93% vs. 94%) but was similar thereafter (mean, 95% in the two groups). • The percentage of pill bottles returned was 66% by 30 days and 86% by 60 days. • Among subjects in the emtricitabine–tenofovir group, at least one of the study-drug components was detected in 3 of 34 subjects with HIV infection (9%) and in 22 of 43 seronegative control subjects (51%).

Grohskopf 2013 (CDC Safety Study)	Tenofovir (daily)	• Adherence was measured by pill count, medication event monitoring system (MEMS) and self-report; adherence ranged from 77% (pill count) to 92% (MEMS).
Kibengo 2013 (IAVI Uganda Study)	Tenofovir/emtricitabine (daily or intermittent)	• Median MEMS adherence rates were 98% (IQR: 93–100) for daily PrEP regimen, 91% (IQR: 73–97) for fixed intermittent dosing and 45% (IQR: 20–63) for post-coital dosing. • There was no difference in adherence rates between active and placebo groups, thus these two groups were combined for the adherence analyses.
Hosek 2013 (Project PrEPare)	Tenofovir/emtricitabine (daily)	• Self-reported medication adherence averaged 62% (range 43–83%) while rates of detectable tenofovir in plasma of participants in the emtricitabine/tenofovir arm ranged from 63.2% (week 4) to 20% (week 24).
Mazzarro 2015 (VOICE)	Tenofovir (oral), tenofovir/emtricitabine (oral) and vaginal tenofovir gel (all daily)	• 90% by self-report, 86% by returned products and 88% as assessed with audio computer-assisted self-interviewing (ACASI). • In a random sample, tenofovir was detected in 30%, 29% and 25% of available plasma samples from participants randomly assigned to receive tenofovir, tenofovir/emtricitabine and tenofovir gel, respectively.
McCormack 2015 (PROUD)	Tenofovir/emtricitabine (daily)	• Overall, sufficient study drug was prescribed for 88% of the total follow-up time. • Tenofovir was detected in plasma of all 52 sampled participants (range 38–549 ng/mL) who reported that they were taking PrEP.
Molina 2015 (Ipergay)*	Tenofovir/emtricitabine (intermittent)	• Median pills per month: 15 pills. • In the tenofovir–emtricitabine group, the rates of detection were 86% for tenofovir and 82% for emtricitabine, respectively, a finding that was consistent with receipt of each drug within the previous week. Tenofovir and emtricitabine were also detected in eight participants in the placebo group, three of whom were receiving postexposure prophylaxis. • Computer-assisted structured interviews also performed to assess most recent sexual episode. Overall, 28% of participants did not take tenofovir-emtricitabine or placebo, 29% took the assigned drug at a suboptimal dose and 43% took the assigned drug correctly.
Mutua 2012 (IAVI Kenya Study)	Tenofovir/emtricitabine (daily or intermittent)	• There was no difference in adherence rates between treatment and placebo groups, thus these groups were combined for the adherence analyses. Median MEMS adherence rates were 83% (IQR: 63–92) for daily dosing and 55% (IQR:28–78) for fixed intermittent dosing (p=0.003).
Peterson 2007 (West Africa Study)	Tenofovir (daily)	• The amount of product used was estimated by subtracting the number of pills returned from the number dispensed, and dividing this number by the total number of days in the effectiveness analysis. • Drug was used no more than 69% of study days. Excluding time off product due to pregnancy, drug was used for no more than 74% of study days.

Thigpen 2012 (TENOFOVIR2)	Tenofovir/emtricitabine (daily)	• The two groups had similar rates of adherence to the study medication as estimated by means of pill counts (84.1% in the tenofovir–emtricitabine group and 83.7% in the placebo group, P = 0.79) and self-reported adherence for the preceding 3 days (94.4% and 94.1%, respectively; P = 0.32). • Among the four participants in the tenofovir–emtricitabine group who became infected with HIV during the study, two (50%) had detectable levels of tenofovir and emtricitabine in plasma obtained at the visit before and closest to their estimated seroconversion dates. Among a small sample who did not undergo seroconversion, 55 (80%) and 56 (81%) had detectable levels of tenofovir and emtricitabine, respectively.
VanDamme 2012 (FEM-PrEP)	Tenofovir/emtricitabine (daily)	• At the time of study-drug discontinuation, 95% of participants reported that they had usually or always taken the assigned drug. Pill-count data were consistent with ingestion of the study drug on 88% of the days on which it was available to the participants. • In contrast, drug-level testing revealed much lower levels of adherence. Among women with seroconversion in the tenofovir–emtricitabine group, the target plasma level of tenofovir was identified in 7 of 27 women (26%) at the beginning of the infection window (excluding six women for whom the window started at enrolment), in 7 of 33 (21%) at the end of the window, and in 4 of 27 (15%) at both visits. Among the uninfected control participants, the numbers of women with target-level tenofovir were somewhat higher: 27 of 78 women (35%) at the beginning of the infection window, 35 of 95 (37%) at the end of the window, and 19 of 78 (24%) at both visits.

Tenofovir = Tenofovir Disoproxil Fumarate

* non-daily regimen

S3.6 Change in sexual behaviour/STI rates

Study	Measure	Outcome
Baeten 2012 (Partners PrEP)	• Having sex without a condom with HIV-positive partners in prior month • STI diagnoses from sex acts outside partnership	• At enrolment, 27% of HIV-1 seronegative partners reported sex without condoms with their HIV-1 seropositive partner during the prior month. This percentage decreased during follow-up (to 13% and 9% at 12 and 24 months) and was similar across the study arms. • The proportion reporting outside partnerships and who acquired sexually transmitted infections during follow up did not differ across the study arms.
Baeten 2014 (Partners PrEP)	Unreported	
Bekker 2018 (ADAPT Cape Town)	Unreported	
Choopanya 2013 (Bangkok Tenofovir Study)	• Drug use behaviour • Number of sexual partners	• Tenofovir and placebo recipients reported similar rates of injecting and sharing needles and similar numbers of sexual partners during follow up with no interactions between time and treatment group. • Overall, number of participants reporting injecting drugs or sharing needles reduced over time. • Sex with more than one partner decreased from 522 (22%) at enrolment to 43 (6%) at month 72.
Grant 2010 (iPrEx)	• Number of anal sex acts • Proportion of anal sex acts with a condom • STI diagnoses	• Sexual practices were similar in the two groups at all time points. • The total numbers of sexual partners with whom the respondent had receptive anal intercourse decreased, and the percentage of those partners who used a condom increased after subjects enrolled in the study. • There were no significant between-group differences in the numbers of subjects with syphilis, gonorrhea, chlamydia, genital warts or genital ulcers during follow-up.
Grohskopf 2013 (CDC Safety Study)	Unreported	
Hosek 2013 (Project PrEPare)	Male-to-male unprotected anal sex acts	• No significant differences among the three treatment groups across visits. • Insignificant trend from baseline to week 24 of decreasing unprotected anal sex acts across all treatment arms.
Kibengo 2013 (IAVI Uganda Study)	HIV behaviour change	• The median number of sexual partners in the past month remained at 1 (IQR: 1–1) during the trial. • No other HIV risk behaviours reported at baseline changed during the trial
Mazzarro 2015 (VOICE)	Unreported	
McCormack 2015 (PROUD)	• Number of sexual partners • Incident STIs	• Total number of different anal sex partners varied widely between baseline and year 1. No significant difference between groups at one year was detected. • Proportion with confirmed rectal chlamydia/gonorrhea was similar in immediate and delayed arms (proxy for condomless anal intercourse). • Adjusted odds ratio for rectal chlamydia or gonorrhea: 1.00 (0.72–1.38) (adjusted for number of sexual health screens)

Molina 2015 (Ipergay)	• Total number of sexual intercourse events • Proportion of events without a condom • Number of sexual partners • Incident STIs	• Sexual practices did not change overall among the participants during the study period as compared with baseline: there were no significant between group differences in the total number of episodes of sexual intercourse in the four weeks before, in the proportion of episodes of receptive anal intercourse without condoms, or in the proportion of episodes of anal sex without condoms during the most recent sexual intercourse. • There was a slight but significant decrease in the number of sexual partners within the past two months in the placebo group as compared with the tenofovir—emtricitabine group (7.5 and 8, respectively; p = 0.001). • The proportions of participants with a new sexually transmitted infection (of the throat, anus, and urinary tract combined) during follow-up were similar, with 41% in the tenofovir—emtricitabine group and 33% in the placebo group (P = 0.10).
Mutua 2012 (IAVI Kenya Study)	HIV behaviour change	• The median number of sexual partners in the past month increased from three (IQR 2–4) at baseline to four (IQR 2–8) at month 4 during the trial. • Because there may have been underreporting of sex partners at baseline, authors also compared the median number of sexual partners month 2 (4) and at month 4 (4).
Peterson 2007 (West Africa Study)	• Condom use at last sex • Number of sex acts • Number of partners	• During screening, participants reported an average of 12 coital acts per week with an average of 21 sexual partners in the previous 30 days (including 11 new partners). During follow-up, participants reported an average of 15 coital acts per week, with an average of 14 sexual partners in the previous 30 days (six new partners). Of note, most participants in this study were sex workers. • Self-reported condom use increased from 52% at screening (average across all sites during the last coital act prior to screening) to approximately 92% at the enrolment, month 3, month 6, and month 9 visits, to 95% at the month 12 visit (for acts occurring during the last seven days). The average condom use during the follow-up period was 92%.
Thigpen 2012 (TENOFOVIR2)	• Protected sex episodes with main/ most recent casual partner • Number of sexual partners	• The percentage of sexual episodes in which condoms were used with the main or most recent casual sexual partner was similar in the two study groups at enrolment (81.4% [range, 76.6 to 86.4] in the tenofovir–emtricitabine group and 79.2% [range, 71.6 to 87.6] in the placebo group, P = 0.66) and remained stable over time. • The reported number of sexual partners declined in both groups during the course of the study.
VanDamme 2012 (FEM-PrEP)	• Number of partners • Sex acts without a condom • Pelvic STIs	• There was no evidence of increased HIV risk behaviour during the trial, with modest but significant reductions in the numbers of partners (mean reduction, 0.14; P<0.001 by paired-data t-test), vaginal sex acts (mean reduction, 0.58; P<0.001), and sex acts without a condom (mean reduction, 0.46; P<0.001) reported by women at the last follow-up visit, as compared with seven days before enrolment.

		• Fewer than half the study participants agreed to undergo a pelvic examination. There were no significant between-group differences in the prevalence of pelvic STIs.

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

	Reporting Item	Page Number
Title		
#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract		

Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	6
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	7
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	8

Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	8
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material 2
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	7
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	8
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	Supplementary Material 2
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	8

Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	9
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	13
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Supplementary Material 2

Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	16-23 and Supplementary Material 2
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	16-23 and Supplementary Material 2
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	GRADE assessment and Supplementary Material 2
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	21
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	25
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	26

Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28

Funding

Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	1

Notes:

- 8: Supplementary Material 2
- 11: Supplementary Material 2
- 19: Supplementary Material 2
- 20: 16-23 and Supplementary Material 2
- 21: 16-23 and Supplementary Material 2
- 22: GRADE assessment and Supplementary Material 2 This checklist was completed on 20. December 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai